

# Reproduktionsmedizin- ein Update der heutigen Möglichkeiten

Fortbildung pharmazeutische Gesellschaft Basel  
Dr. med. Alexander Quaas  
Medical Director, Shady Grove Fertility San Diego  
Leitender Arzt Reproduktionsmedizin und gyn.  
Endokrinologie 2021-2023  
San Diego / Basel, 19. März 2024



# Reproduktionsmedizin- ein Update der heutigen Möglichkeiten

---

## Struktur

---

Historische Aspekte

---

Das Spektrum reproduktionsmedizinischer Behandlungen

---

Geografische Unterschiede und Kontroversen

---

Pharmazeutische Aspekte

---

Elective oocyte cryopreservation («Social Freezing»)

---

Take-home points

---

---

---

---

---

---

---

---

---

---

And here she is...

# THE LOVELY LOUISE



**LOUISE BROWN, bright-eyed at 18 hours old: The test tube baby in hospital yesterday**

Daily Mail World Exclusive Picture by Bill Cross © World Copyright Associated Newspapers Group Ltd., 1978. Full story and more pictures inside

Daily Mail,  
27.07.1978

# Letter to editor (Lancet, 1978)

## Letters to the Editor

### BIRTH AFTER THE REIMPLANTATION OF A HUMAN EMBRYO

SIR, — We wish to report that one of our patients, a 30-year-old nulliparous married woman, was safely delivered by caesarean section on July 25, 1978, of a normal infant girl weighing 2700 g. The patient had been referred to one of us (P.C.S.) in 1976 with a history of 9 years' infertility, tubal occlusions, and unsuccessful salpingostomies done in 1970 with excision of the ampullae of both oviducts followed by persistent tubal blockages. Laparoscopy in February, 1977, revealed grossly distorted tubal remnants with occlusion and peritubal and ovarian adhesions. Laparotomy in August, 1977, was done with excision of the remains of both tubes, adhesiolysis, and suspension of the ovaries in good position for oocyte recovery.

Pregnancy was established after laparoscopic recovery of an oocyte on Nov. 10, 1977, in-vitro fertilization and normal cleavage in culture media, and the reimplantation of the 8-cell embryo into the uterus 2 $\frac{1}{2}$  days later. Amniocentesis at

16 weeks' pregnancy revealed normal  $\alpha$ -fetoprotein levels, with no chromosome abnormalities in a 46 XX fetus. On the day of delivery the mother was 38 weeks and 5 days by dates

from her last menstrual period, and she had pre-eclamptic toxæmia. Blood-pressure was fluctuating around 140/95, œdema involved both legs up to knee level together with the abdomen, back, hands, and face; the blood-uric-acid was 390  $\mu\text{mol/l}$ , and albumin 0.5 g/l of urine. Ultrasonic scanning and radiographic appearances showed that the fetus had grown slowly for several weeks from week 30. Blood-œstriols and human placental lactogen levels also dropped below the normal levels during this period. However, the fetus grew considerable during the last 10 days before delivery while placental function improved greatly. On the day of delivery the biparietal diameter had reached 9.6 cm, and 5 ml of amniotic fluid was removed safely under sonic control. The lecithin: sphingomyelin ratio was 3.9:1, indicative of maturity and low risk of the respiratory-distress syndrome.

We hope to publish further medical and scientific details in your columns at a later date.

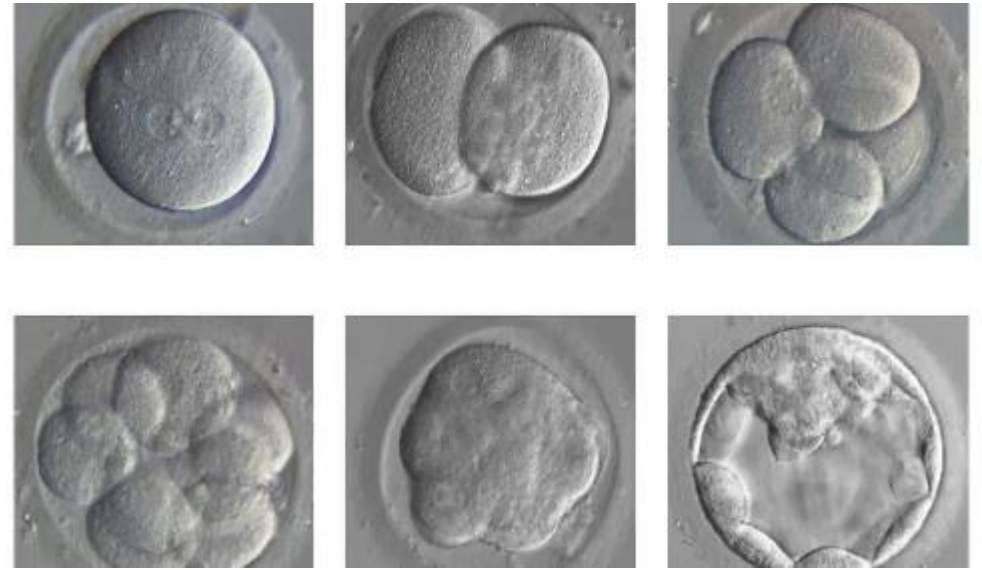
Department of  
Obstetrics and Gynaecology,  
General Hospital,  
Oldham OL1 2JH

P. C. STEPTOE

University Physiology Laboratory,  
Cambridge CB2 3EG

R. G. EDWARDS

# IVF: die Anfänge



- “Natural cycle”
- Laparoskopische Eizellentnahme (teils mitten in der Nacht)
- «Konventionelle» Befruchtung- Inkubation Spermien / Eizelle
- Transfer nach 2-3 Tagen: «cleavage stage»

# Edwards / Steptoe / Purdy BJOG 1980

## British Journal of Obstetrics and Gynaecology

Vol 87 No. 9

NEW SERIES

SEPTEMBER 1980

### ESTABLISHING FULL-TERM HUMAN PREGNANCIES USING CLEAVING EMBRYOS GROWN *IN VITRO*\*

BY

R. G. EDWARDS

P. C. STEPTOE

AND

J. M. PURDY

*Physiological Laboratory, Cambridge University and the  
Oldham General Hospital, Oldham*

#### Summary

The establishment of human pregnancies by the use of fertilization *in vitro* and placing cleaving embryos into the uterus is described. Preovulatory oocytes were aspirated at laparoscopy from the ovaries of patients soon after the beginning of the mid-cycle surge of luteinizing hormone (LH) during the natural cycle. The LH surge was identified by assaying 3-hourly samples of urine, and measurements of oestrogens in 24-hour samples were used to assess follicular growth. The surge of LH was identified in 68 patients and it showed a diurnal rhythm. Preovulatory oocytes were aspirated from most of the patients. Fertilization and cleavage occurred in 34 instances, and 32 embryos were put into the mother via the cervical canal. Four patients became pregnant. There were indications that a diurnal rhythm played a role in establishing cleaving embryos, each of the four pregnancies occurring when the embryos were placed in late evening. Each of the pregnancies resulted from oocytes which were aspirated from their follicles 24 hours or longer after the LH surge began. Details are given of three abortive pregnancies in patients given gonadotrophins to stimulate the maturation of oocytes used for fertilization *in vitro*.

The comparative failure of attempts to establish pregnancy following the use of hMG and hCG indicated that an alternative approach was needed, avoiding the use of exogenous hormones. We decided to monitor the natural menstrual cycle of a group of patients, aspirate the single oocyte maturing naturally during mid-cycle, and to put the embryo into the mother during her natural luteal phase.

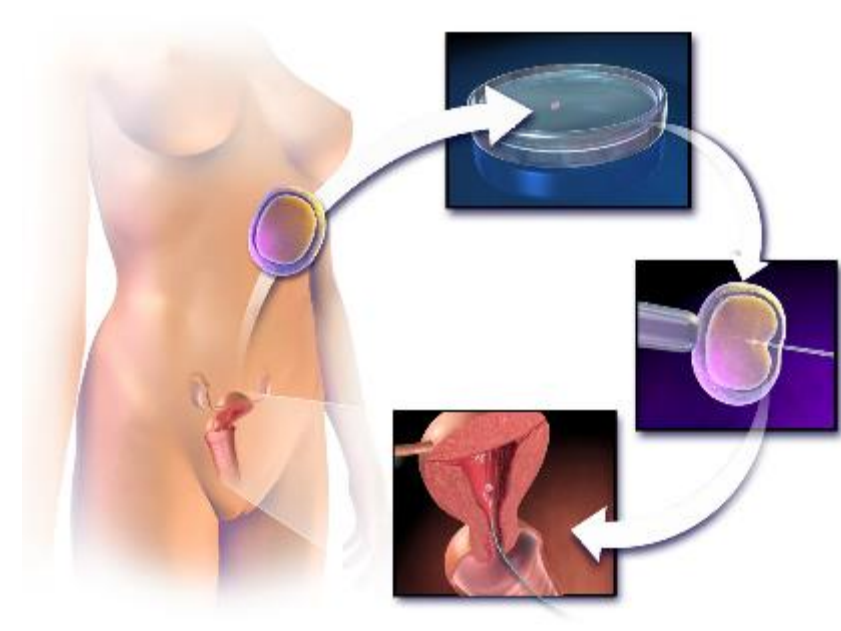
In retrospect, it is clear that the endocrine disturbances following the use of hMG and hCG to induce follicular growth and luteinization in cyclic women were perhaps too much to overcome, and this method may have been abandoned permanently in favour of monitoring the natural menstrual cycle. Why cyclic women respond so abnormally to gonadotrophins is not clear; amenorrhoeic women can be treated with



San Antonio, TX  
Oktober 2017

# IVF 45 Jahre nach Louise's Geburt

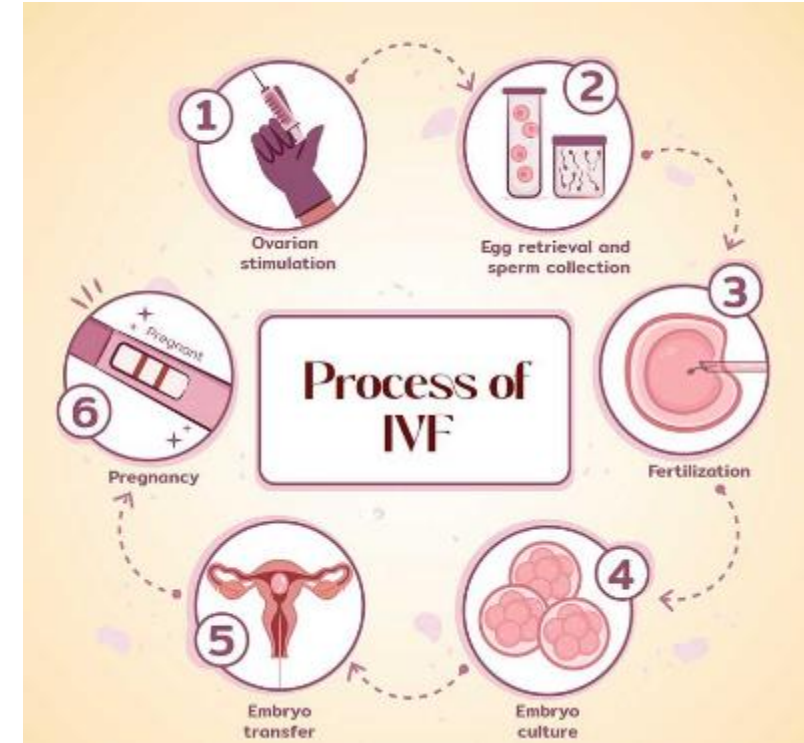
- Ovarielle Stimulation: standard
- Eizellentnahme: transvaginal, ultraschallgesteuert
- Embryo-Transfer im Blastozystenstadium
- Kryopräservierung von Spermien / Eizellen / Embryos möglich
- Genetische Untersuchung der Embryonen: PGT-A und PGT-M
- «Third party reproduction»





# IVF: Bestandteile

- Downregulation / Synchronisierung der Follikel
- Ovarielle Stimulation (+/- "Add-ons")
- Vermeidung einer vorzeitigen Ovulation
- Auslösung des Eisprungs (der Oozyten-Reifung)
- *Frisch-Transfer*: Lutealphasen-Unterstützung
- *freeze-only / freeze-all*: FET (frozen embryo transfer)
  - programmiert oder natürlicher Zyklus



# IVF: Bezug zur Veterinärmedizin

- Erste erfolgreiche IVF-Behandlungen: in Hasen und anderen Tieren
- Conservation efforts: bedrohte Tierarten, z.B White Rhino



- Nur noch 2 Northern White Rhinos auf der Welt
- Zelllinien → Stammzellen → Keimzellen → Embryos

# «Save the chubby unicorns»



**San Diego Zoo  
Wildlife Alliance**

# Grundlage: die Fortpflanzung des Menschen

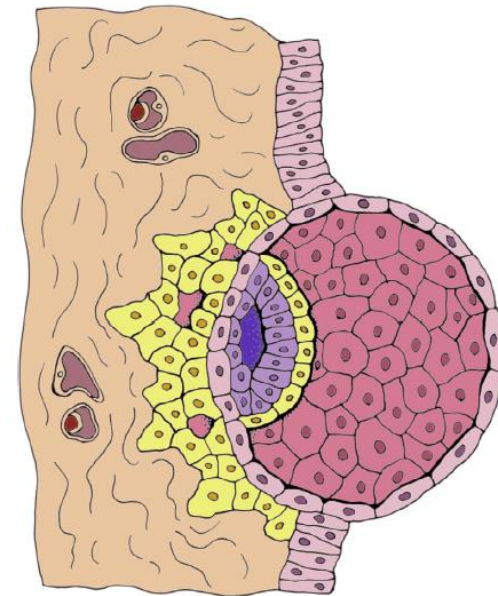
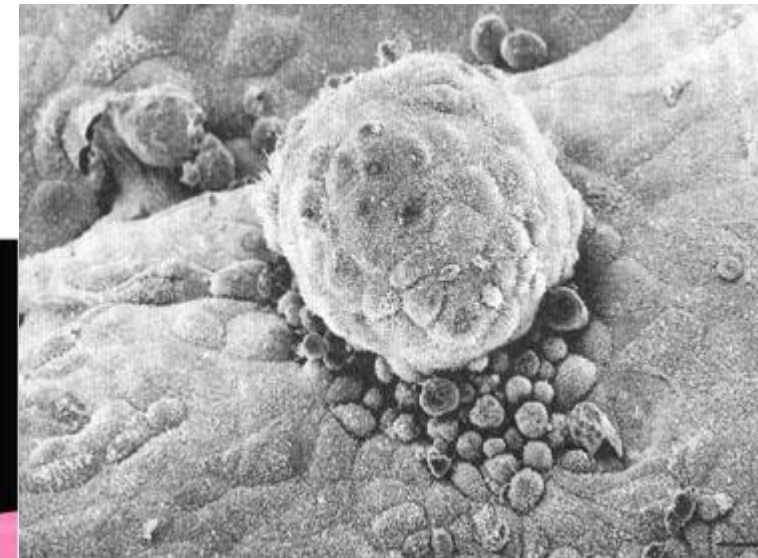
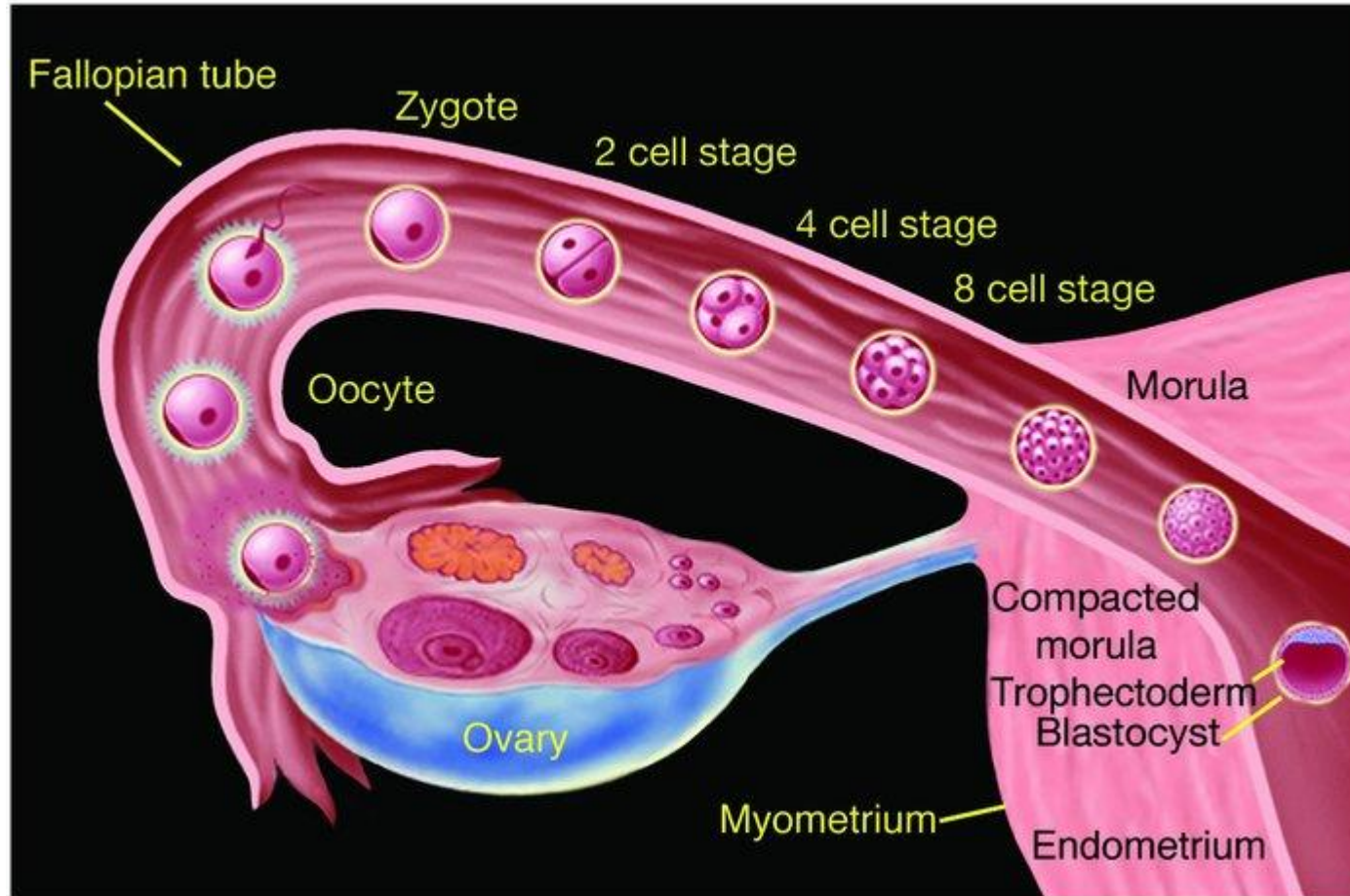
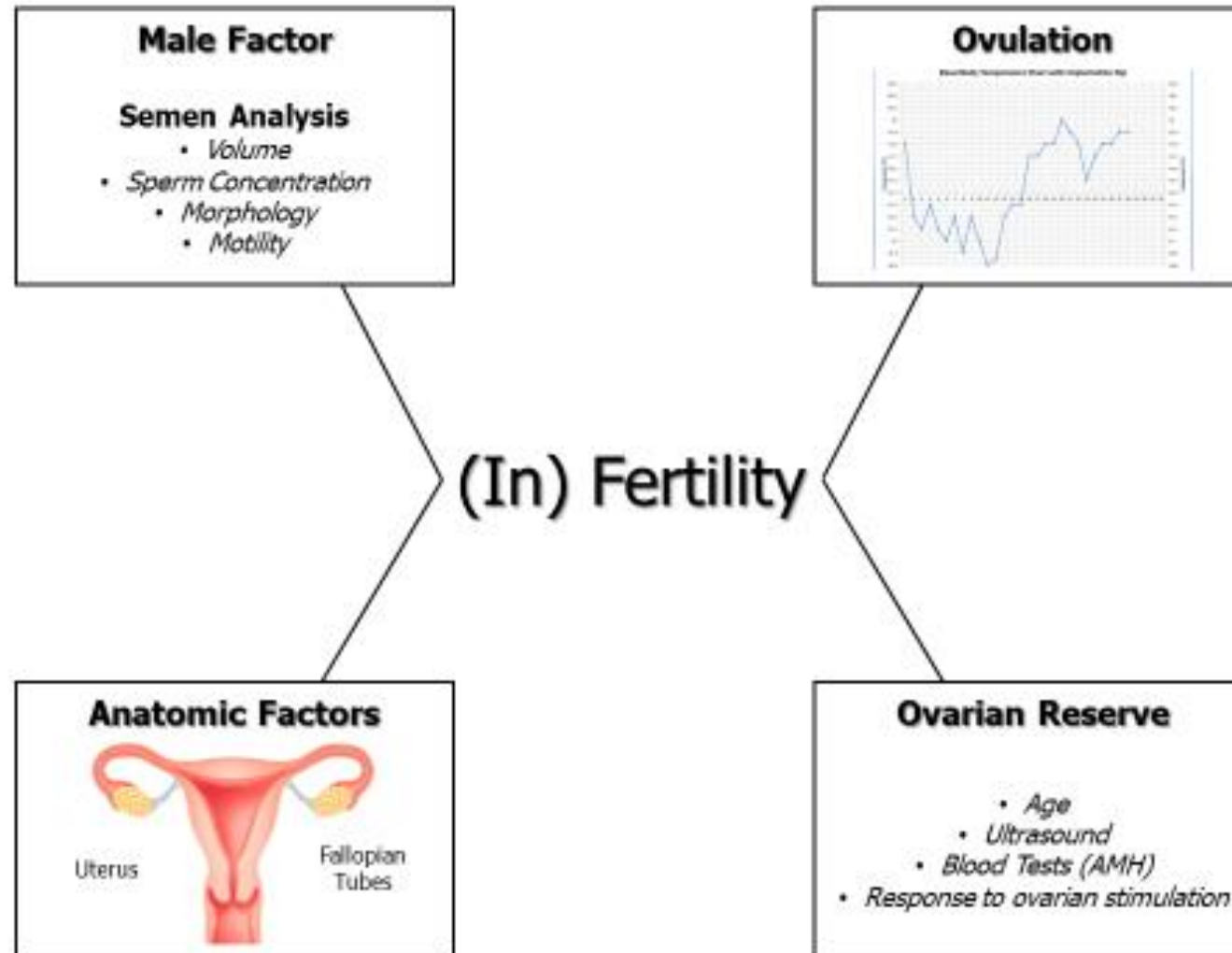


Figure 1 The initial stage of implantation, when the embryo is invading the epithelial layer of the endometrium to be embedded in the stroma compartment.

# Reproduktionsmedizin: Wichtige Komponenten (Diagnostik und Therapie)



# 30%: «Ungeklärte Unfruchtbarkeit»

## DIAGNOSTIC AND TREATMENT UPDATE

### Diagnosis and Treatment of Unexplained Infertility

Alexander Quaas, MD, PhD,\* Anuja Dokras, MD, PhD<sup>†</sup>

\*Brigham and Women's Hospital, Boston, MA; <sup>†</sup>University of Pennsylvania, Philadelphia, PA

Over the past decade, significant advances have occurred in the diagnosis and treatment of reproductive disorders. In this review, we discuss the routine testing performed to diagnose unexplained infertility. We also discuss additional testing, such as assessment of ovarian reserve, and the potential role of laparoscopy in the complete workup of unexplained infertility. Finally, we outline the available therapeutic options and discuss the efficacy and the cost-effectiveness of the existing treatment modalities. The optimal treatment strategy needs to be based on individual patient characteristics such as age, treatment efficacy, side-effect profile, and cost considerations.

[Rev Obstet Gynecol. 2008;1(2):69-76]

© 2008 MedReviews, LLC

Key words: Infertility, unexplained • Semen analysis • Ovulation assessment • Ovarian reserve • Intrauterine insemination • Controlled ovarian hyperstimulation • In vitro fertilization

Criteria	Parameters
Volume	2.0-5.0 mL
pH	7.2-7.8
Sperm concentration	≥ 20 × 10 <sup>6</sup> /mL
Total sperm count	
Motility	
Morphology	
Viability	
White blood cells	
Fructose (total)	

Adapted from *Ann Ist Super Sai*

Figure 1. An example of a basal body temperature recording chart. Reprinted with permission from Hyde and DeLamater, *Understanding Human Sexuality*, 6th ed. Copyright ©1997 The McGraw-Hill Companies, Inc. All rights reserved.

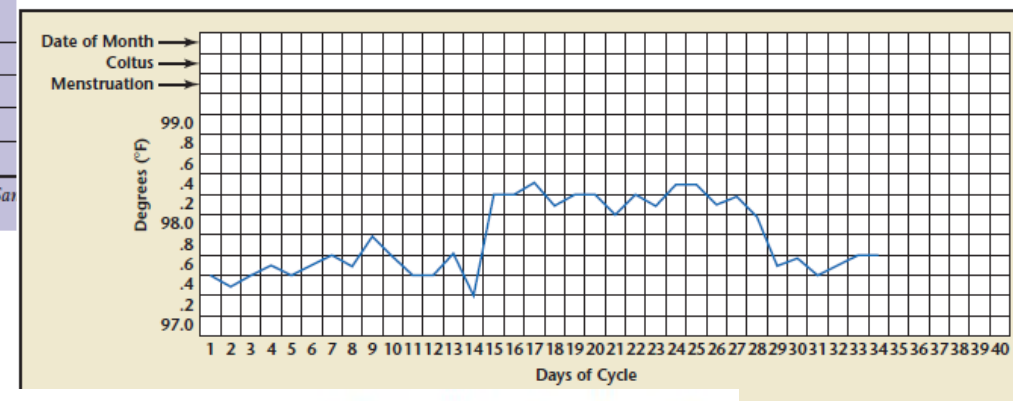
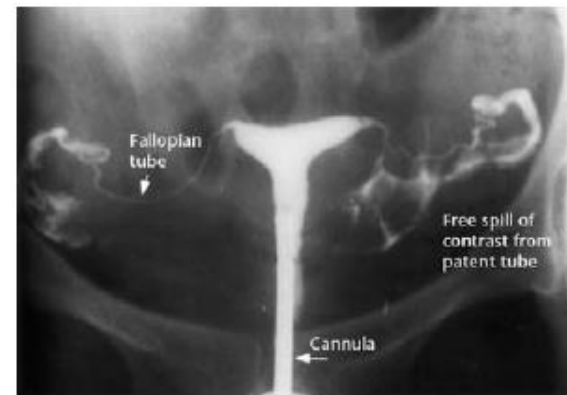


Figure 2. Normal hysterosalpingogram. Reprinted from *Fertility and Sterility*, Volume 83, Baramki TA, *Hysterosalpingography*, pages 1595-1606, Copyright 2005, with permission from Elsevier.



# Das Spektrum der reproduktionsmedizinischen Behandlungen

- Falls möglich: **ursachenbezogen**

- Korrektur von Schilddrüsenerkrankung zur Wiederherstellung ovulatorischer Zyklen

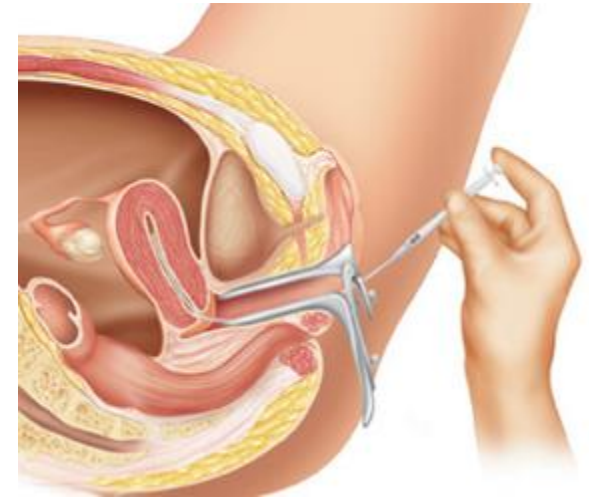
- Absetzen Testosteron-Einnahme bei iatrogenischer Azoospermie

- **Intrauterine Insemination:** autolog oder heterolog (Samenspende)

- **Assisted Reproductive Technology (ART): IVF / ICSI**

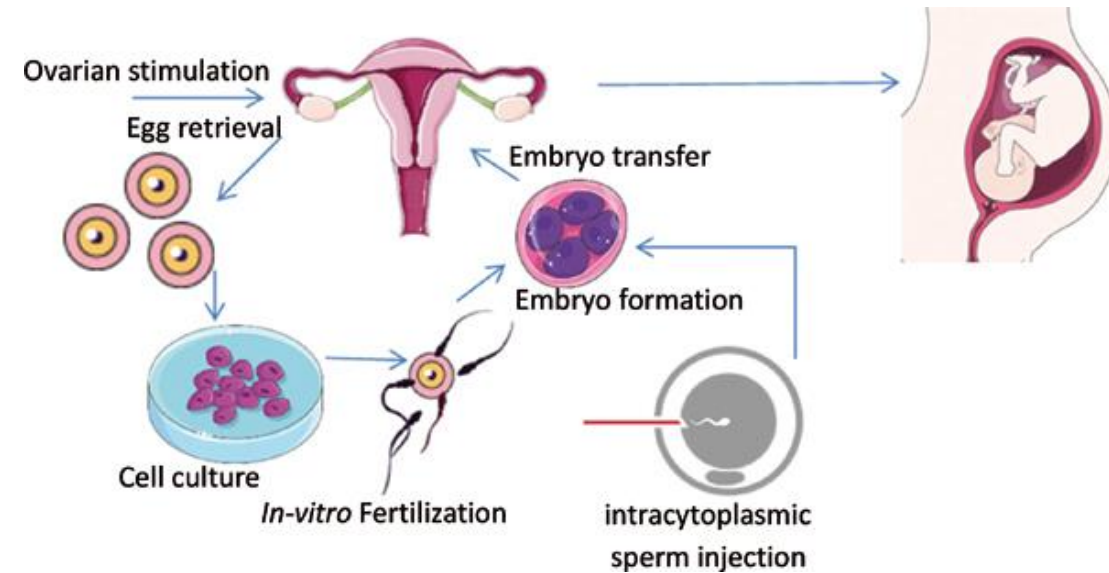
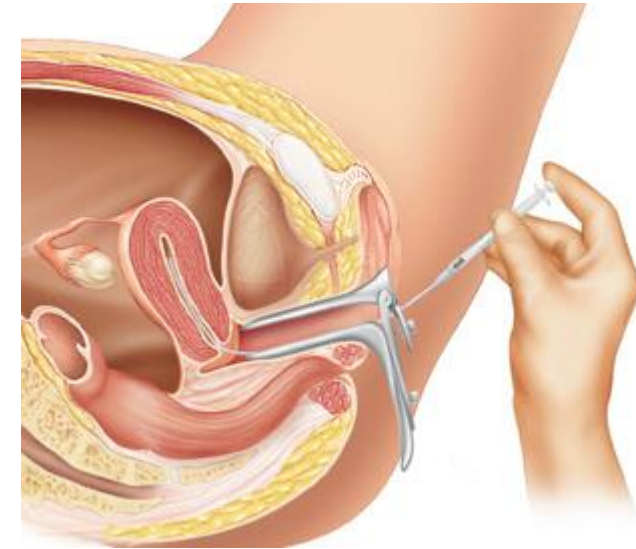
- Autolog

- Heterolog: «Third party reproduction» (Eizellspende, Leihmutterschaft)



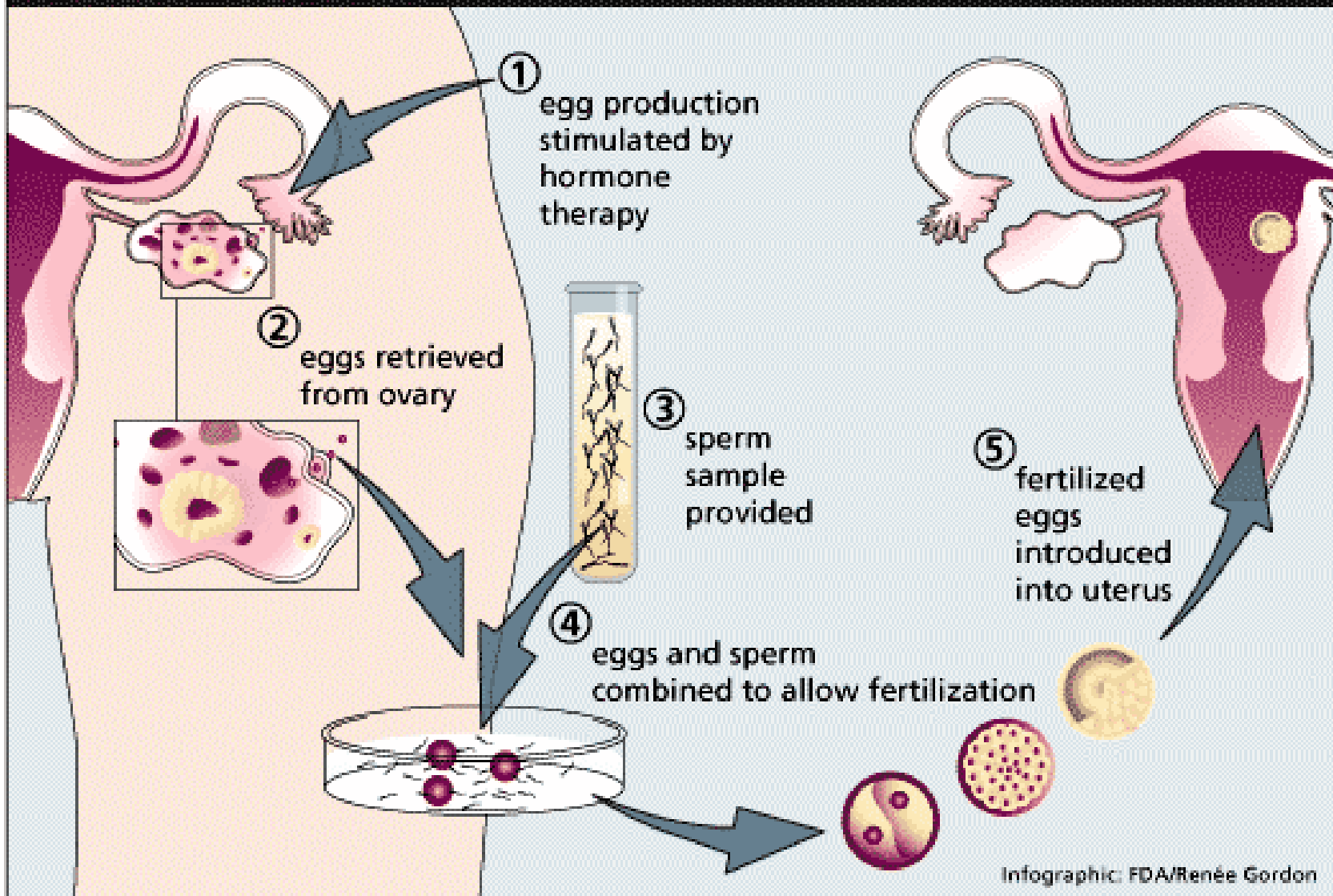
# IUI und IVF

- Intrauterine Insemination (IUI)
- In-vitro fertilization (IVF)
- Intrazytoplasmatische Spermieninjektion (ICSI)





# In Vitro Fertilization



# Ovarielle Stimulation (OS)



3

## Pharmacology of medications used for ovarian stimulation



Alexander M. Quaas, MD <sup>a, b, c, \*</sup>, Richard S. Legro, MD <sup>d</sup>

<sup>a</sup> University Hospital, University of Basel, Clinic for Reproductive Medicine and Gynecologic Endocrinology, Basel, Switzerland

<sup>b</sup> Reproductive Partners San Diego, San Diego, CA, USA

<sup>c</sup> Division of Reproductive Endocrinology and Infertility, University of California, San Diego, CA, USA

<sup>d</sup> Department of Obstetrics and Gynecology, Penn State University College of Medicine, Hershey, PA, USA

*The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, gonadotropins, and pulsatile gonadotropin releasing hormone (GnRH). Novel potential compounds and adjuvant treatment approaches are also discussed, such as kisspeptin agonists and androgens.*

- Orale Medikamente- zB Clomiphen oder Letrozol
- Injizierte Medikamente- v.a. Gonadotropine (FSH / LH / hCG)
- Wichtige Unterscheidung: OS versus *Ovulationsinduktion* bei anovulatorischen Patientinnen
- Intention in diesem Zusammenhang: Induktion multipler reifer Follikel zur Erhöhung der SS-Wahrscheinlichkeit

# Ovulationsinduktion bei PCOS: «PPCOS II»

In 2014, 750 women with polycystic ovary syndrome according to modified Rotterdam criteria were randomly assigned to receive letrozole or clomiphene for up to five treatment cycles in a double-blind, multicenter trial [37]. The cumulative live birth rate was 27.5% in the letrozole arm versus 19.1% in the clomiphene arm ( $P = 0.007$ ); rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87, Fig. 1 [37]).

There was no significant difference in the rates of overall congenital anomalies, pregnancy loss or twin pregnancy. Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. The authors concluded that letrozole was

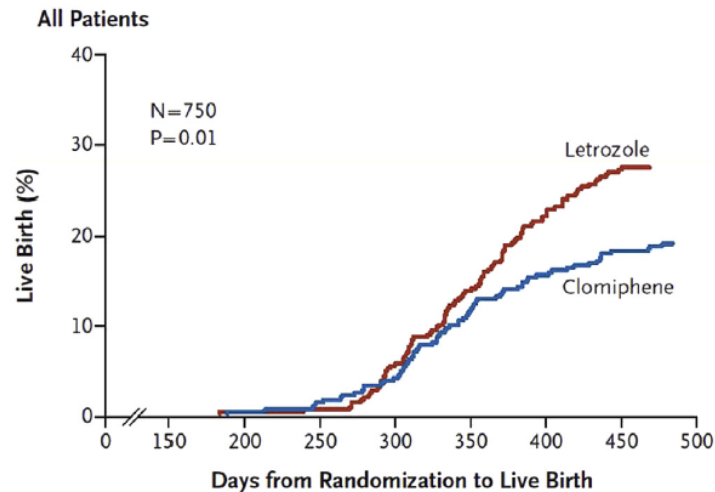


Fig. 1. Kaplan–Meier curves for live birth according to treatment group [37].



ELSEVIER

Contents lists available at ScienceDirect

Best Practice & Research Clinical  
Endocrinology & Metabolism

journal homepage: [www.elsevier.com/locate/beem](http://www.elsevier.com/locate/beem)



3

## Pharmacology of medications used for ovarian stimulation



Alexander M. Quaas, MD<sup>a, b, c, \*</sup>, Richard S. Legro, MD<sup>d</sup>

<sup>a</sup> University Hospital, University of Basel, Clinic for Reproductive Medicine and Gynecologic Endocrinology, Basel, Switzerland

<sup>b</sup> Reproductive Partners San Diego, San Diego, CA, USA

<sup>c</sup> Division of Reproductive Endocrinology and Infertility, University of California, San Diego, CA, USA

<sup>d</sup> Department of Obstetrics and Gynecology, Penn State University College of Medicine, Hershey, PA, USA

The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, gonadotropins, and pulsatile gonadotropin releasing hormone (GnRH). Novel potential compounds and adjuvant treatment approaches are also discussed, such as kisspeptin agonists and androgens.

# Gonadotropine: Grundsteine der ART-Behandlung

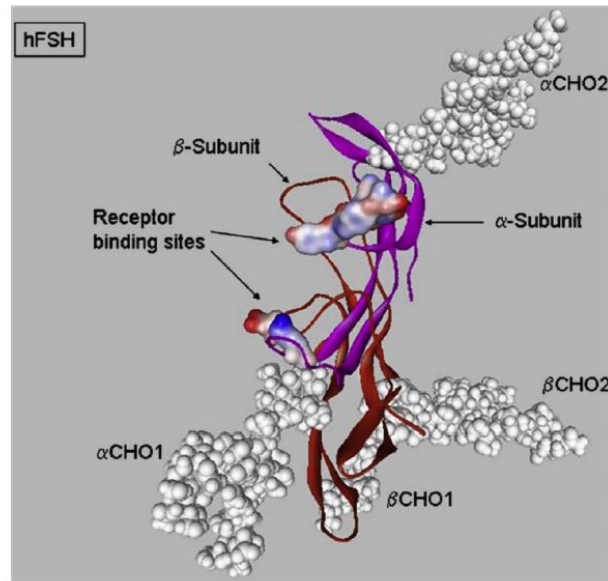


Fig. 2. Biochemical structure of human follicle-stimulating hormone (hFSH),  $\alpha$ -subunit shown in purple,  $\beta$ -subunit shown in red [47].

3

## Pharmacology of medications used for ovarian stimulation



Alexander M. Quaas, MD<sup>a, b, c, \*</sup>, Richard S. Legro, MD<sup>d</sup>

<sup>a</sup> University Hospital, University of Basel, Clinic for Reproductive Medicine and Gynecologic Endocrinology, Basel, Switzerland

<sup>b</sup> Reproductive Partners San Diego, San Diego, CA, USA

<sup>c</sup> Division of Reproductive Endocrinology and Infertility, University of California, San Diego, CA, USA

<sup>d</sup> Department of Obstetrics and Gynecology, Penn State University College of Medicine, Hershey, PA, USA

The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, gonadotropins, and pulsatile gonadotropin releasing hormone (GnRH). Novel potential compounds and adjuvant treatment approaches are also discussed, such as kisspeptin agonists and androgens.

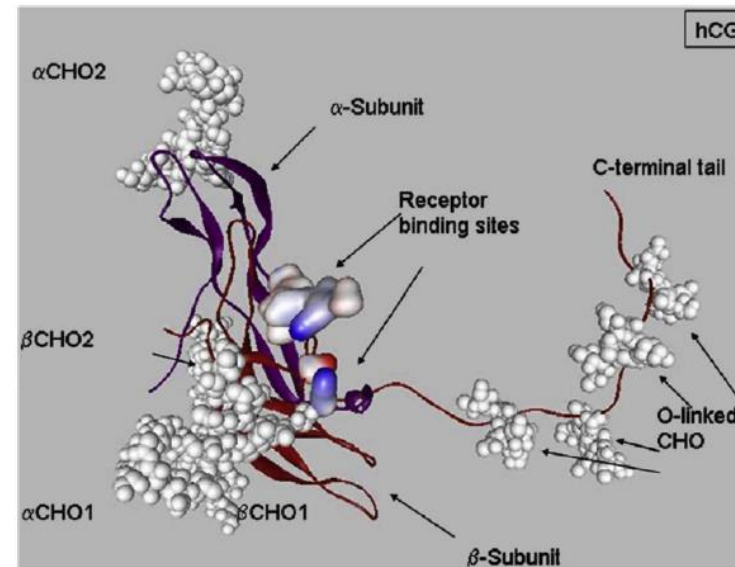
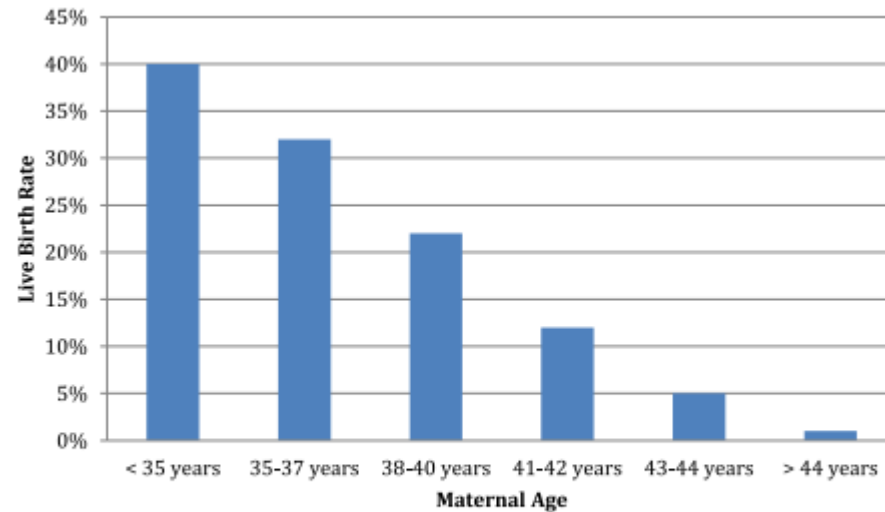
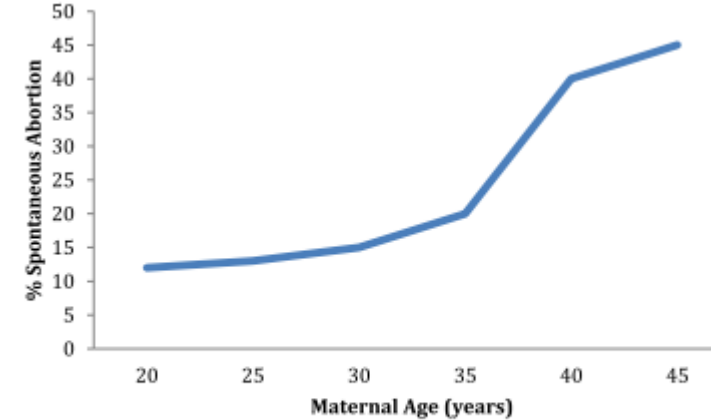


Fig. 3. Biochemical structure of human chorionic gonadotropin (hCG),  $\alpha$ -subunit shown in purple,  $\beta$ -subunit shown in red [47].

# Reproduktives Altern: ↓Erfolgschance mit autologer IVF-Therapie

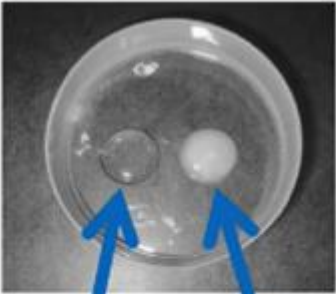
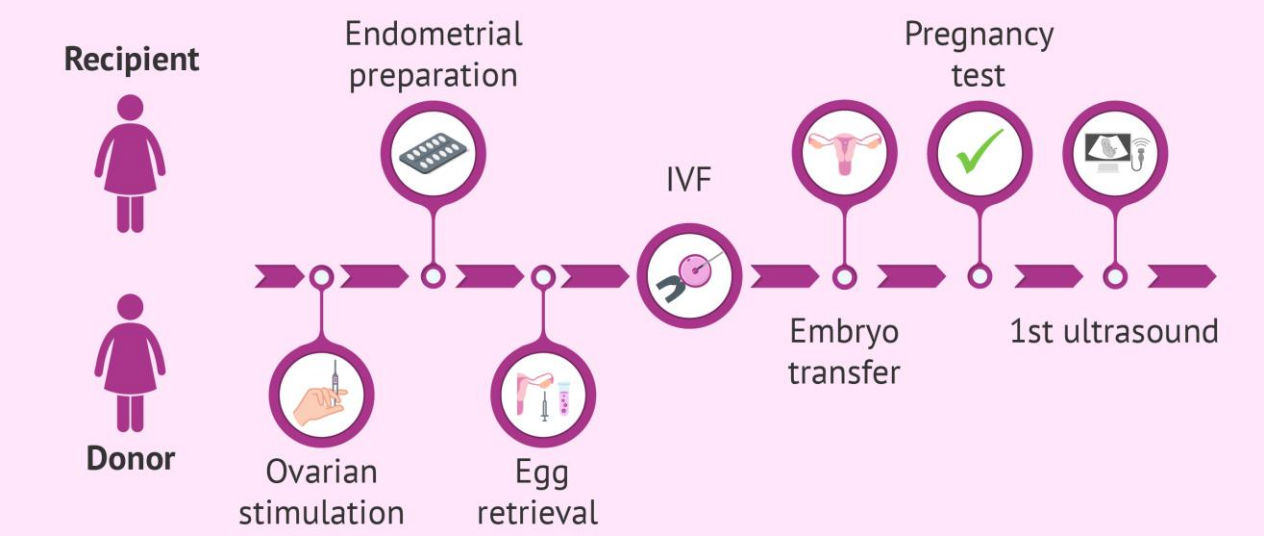


**Fig. 2.** Live birth rates per IVF cycle. (Data from Centers for Disease Control and Prevention, American Society for Reproductive Medicine Society for Assisted Reproductive Technology. 2011 assisted reproductive technology: national summary report. Atlanta (GA): Centers for Disease Control and Prevention; 2013.)



**Fig. 1.** Spontaneous abortions by maternal age. (Data from Hassold T, Chiu D. Maternal age-specific rates of numerical chromosomal abnormalities with specific reference to trisomy. Hum Genet 1985;70:11-17.)

# Eizellspende: Ablauf / Prinzip



Vitrified drop  
(glass)

Frozen drop  
(ice)



# Reproduktionsmedizin: Fachbereich mit den grössten geografischen Unterschieden von allen



Reproduktionsmedizinische Versorgung:  
lokales Privileg, kein universelles Anrecht

Journal of Assisted Reproduction and Genetics (2018) 35:1559–1563  
<https://doi.org/10.1007/s10815-018-1249-7>

COMMENTARY



Local privileges not universal rights: geographic variations in the science and clinical practice of reproductive medicine

Alexander M. Quaas<sup>1,2,3,4</sup>

Received: 16 May 2018 / Accepted: 21 June 2018 / Published online: 4 July 2018  
© Springer Science+Business Media, LLC, part of Springer Nature 2018

## Abstract

Based on personal experience in the science and clinical practice of reproductive medicine in different settings, enormous variations are highlighted, demonstrating that freedom of research and clinical practice in reproductive medicine is a local privilege, not a universal right.

# Warum gibt es so grosse Unterschiede?



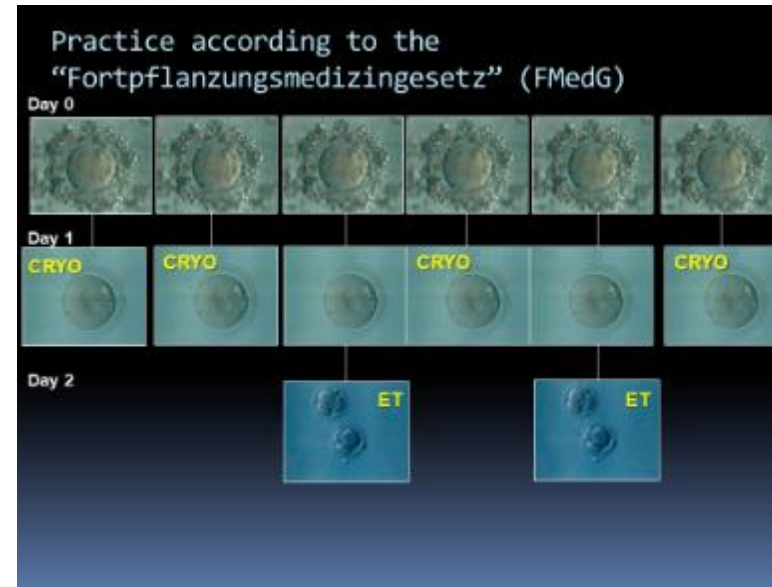
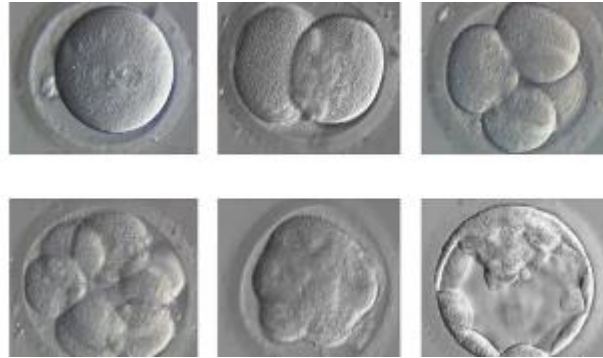
## Viele Faktoren

- Kulturell
- Legal
- Gesundheitssystem-spezifisch
- «That's how we have always done it»





# Beispiel: Schweiz



Bis September 2017: restriktives «Fortpflanzungsmedizingesetz» (FMedG)

- Kern des Gesetzes: es dürfen nur so viele «imprägnierte Eizellen» weiter als Embryos kultiviert werden, wie direkt übertragen werden können
- Kryokonservierung also nur im Vorkernstadium möglich, nicht als Blastozysten
- Folge: schlechte Schwangerschaftsraten, hohes Mehrlingsrisiko
- Volksabstimmung Juni 2016

# Volksabstimmung 2016

Vorher:

## ■ VERBOTEN

- Embryokultur von > 3 «imprägnierten Eizellen»
- Blastozysten-Kryo
- Prä-Implantationsdiagnose
- Eizellspende und Leihmutterschaft
- Behandlung von singles und gleichg. Paaren

## ■ ERLAUBT

- Einfrieren von «imprägnierten Eizellen»
- Polkörperanalyse
- Samenspende (nur verheiratete Paare!)
- Unfruchtbarkeitstherapie für unverheiratete heterosexuelle Paare



Juni 2016:  
62-38% für JA



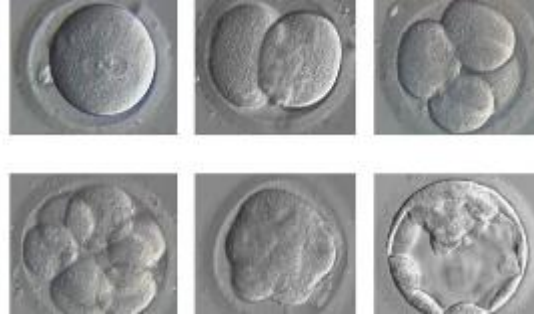
## ■ VERBOTEN

- Embryokultur von > 12 «imprägnierten Eizellen»
- Eizellspende und Leihmutterschaft
- Behandlung von singles und gleichg. Paaren
- (reproduktives Klonen)

## ■ ERLAUBT

- Blastozysten-Kryo
- PGT-A
- Samenspende (nur verheiratete Paare!)
- Unfruchtbarkeitstherapie für unverheiratete heterosexuelle Paare

# Ergebnis: bessere reproduktive Versorgung



Gynäkologische Endokrinologie 2021 · 19:156–159  
<https://doi.org/10.1007/s10304-020-00369-0>  
Angenommen: 9. Dezember 2020  
Online publiziert: 7. Januar 2021  
© Der/die Autor(en) 2021

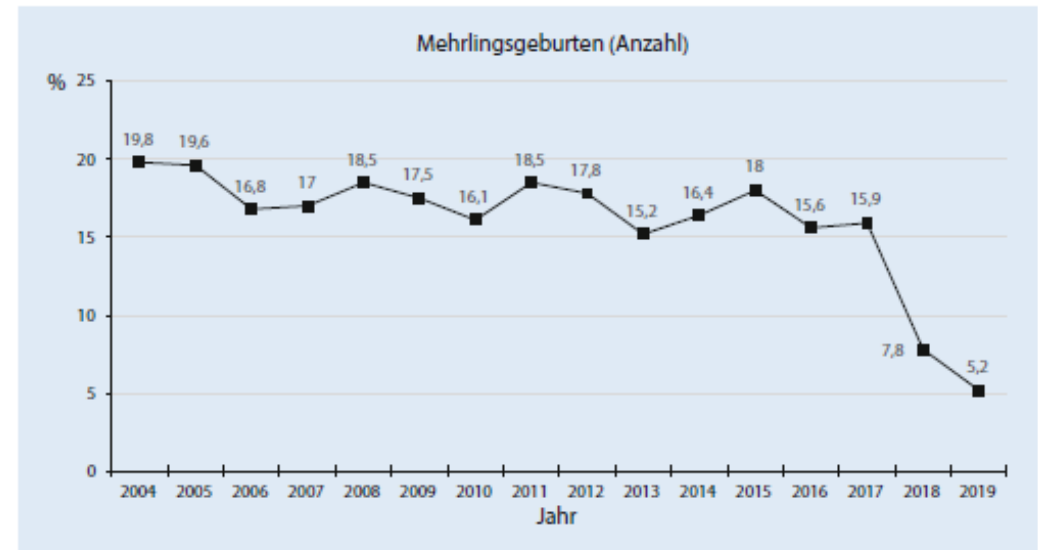
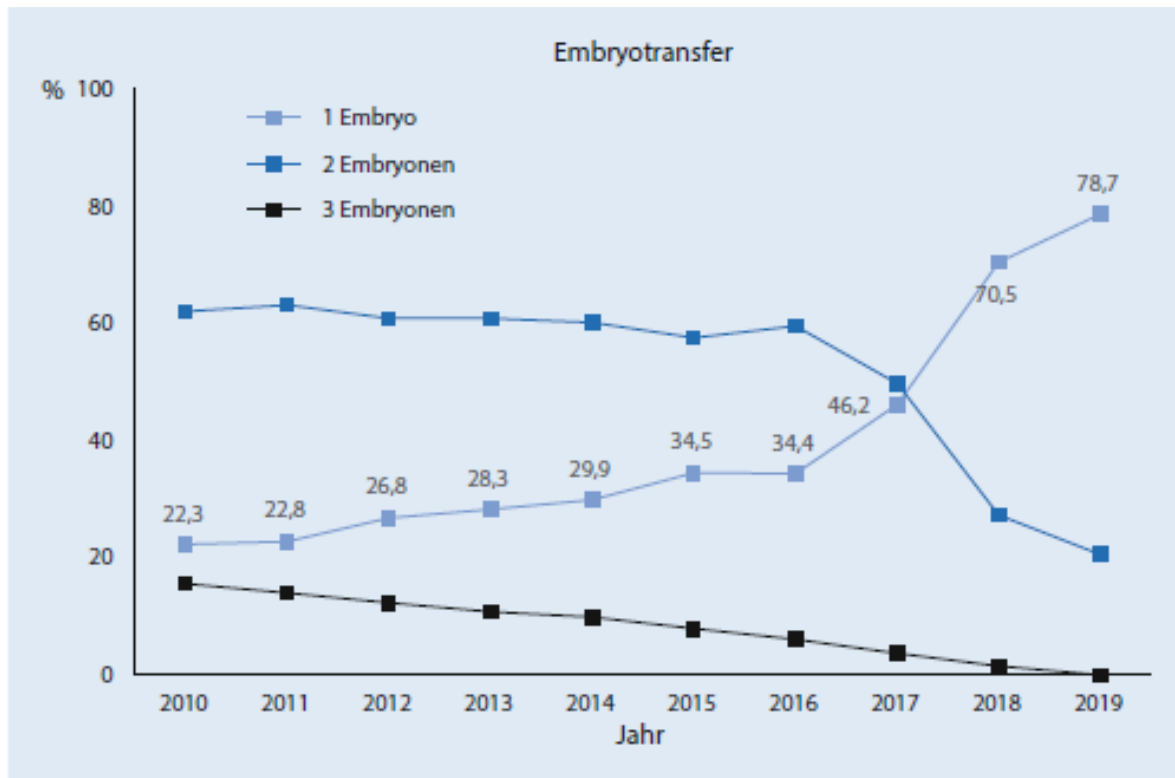
C. De Geyter

Reproduktionsmedizin und gynäkologische Endokrinologie (RME), Universitätsspital Basel, Basel, Schweiz

H. Kentenich, Berlin  
W. Küpker, Baden-Baden  
S. Tschudin, Basel  
L. Wildt, Innsbruck



## Änderung des Fortpflanzungs- medizingesetzes und daraus resultierende Entwicklungen in der Schweiz



➤ ↑ «single embryo transfer», ↓ Risiko Mehrlingsschwangerschaften

# Andere Länder: Beispiele

- 6 Zyklen von der KK übernommen
- KK-übernahme an eSET gekoppelt
- Eizellspende / PGT-A erlaubt
- «Reproductive tourists»: gleichgeschlechtliche Paare aus Frankreich, deutsche Paare interessiert an Blastozysten-Kryo etc.



- Unterschiedliche Regeln je nach «province»
- Eizellspende / PGT-A erlaubt
- Behandlung von singles und gleichg. Paaren: erlaubt
- Leihmutterschaft toleriert
- 98% single embryo transfer



PRACE ORYGINALNE  
*niepłodność*

Reproductive outcomes of intracytoplasmic sperm injection (ICSI) in good-prognosis patients who electively decided to limit the number of oocytes used for microinjection: a two-center comparative study

Ograniczenie liczby komórek jajowych wykorzystanych w docytoplazmatycznej iniekcji plemnika (ICSI) nie pogarsza wyników leczenia metodą zapłodnienia pozaustrojowego: dwuśrodkowe badanie porównawcze

- Polnische Studie: ähnliche Outcomes wenn nur bis zu 6 Eizellen befruchtet werden
- Gesetz eingeführt: maximal 6 Oozyten befruchtet



- Sehr grosszügige Kostenübernahme
- Eizellspende / PGT-A erlaubt
- «Gender selection» bei  $\geq 4$  Kindern des gleichen Geschlechts, spezieller Antrag notwendig
- Einfluss der verschiedenen Religionen auf die Therapie (zB orthodox)



# «European Atlas of Fertility Treatment Policies»

## TIME FOR A EUROPEAN GAME-CHANGING MOVEMENT ON INFERTILITY



In the European Union alone **25 million** citizens face infertility



Infertility affects **1 in 6 couples** worldwide

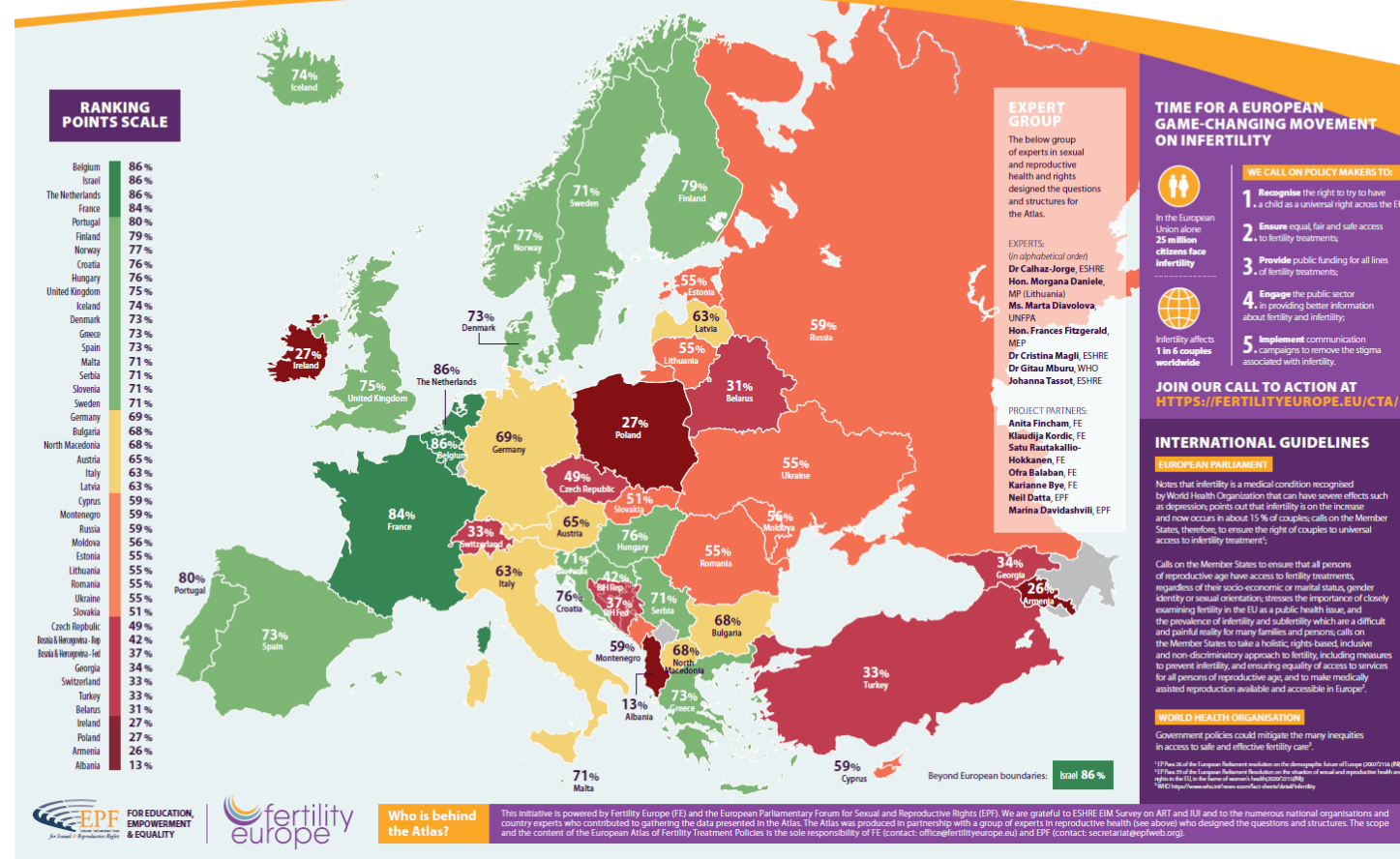
### WE CALL ON POLICY MAKERS TO:












- 1. Recognise** the right to try to have a child as a universal right across the EU;
- 2. Ensure** equal, fair and safe access to fertility treatments;
- 3. Provide** public funding for all lines of fertility treatments;
- 4. Engage** the public sector in providing better information about fertility and infertility;
- 5. Implement** communication campaigns to remove the stigma associated with infertility.

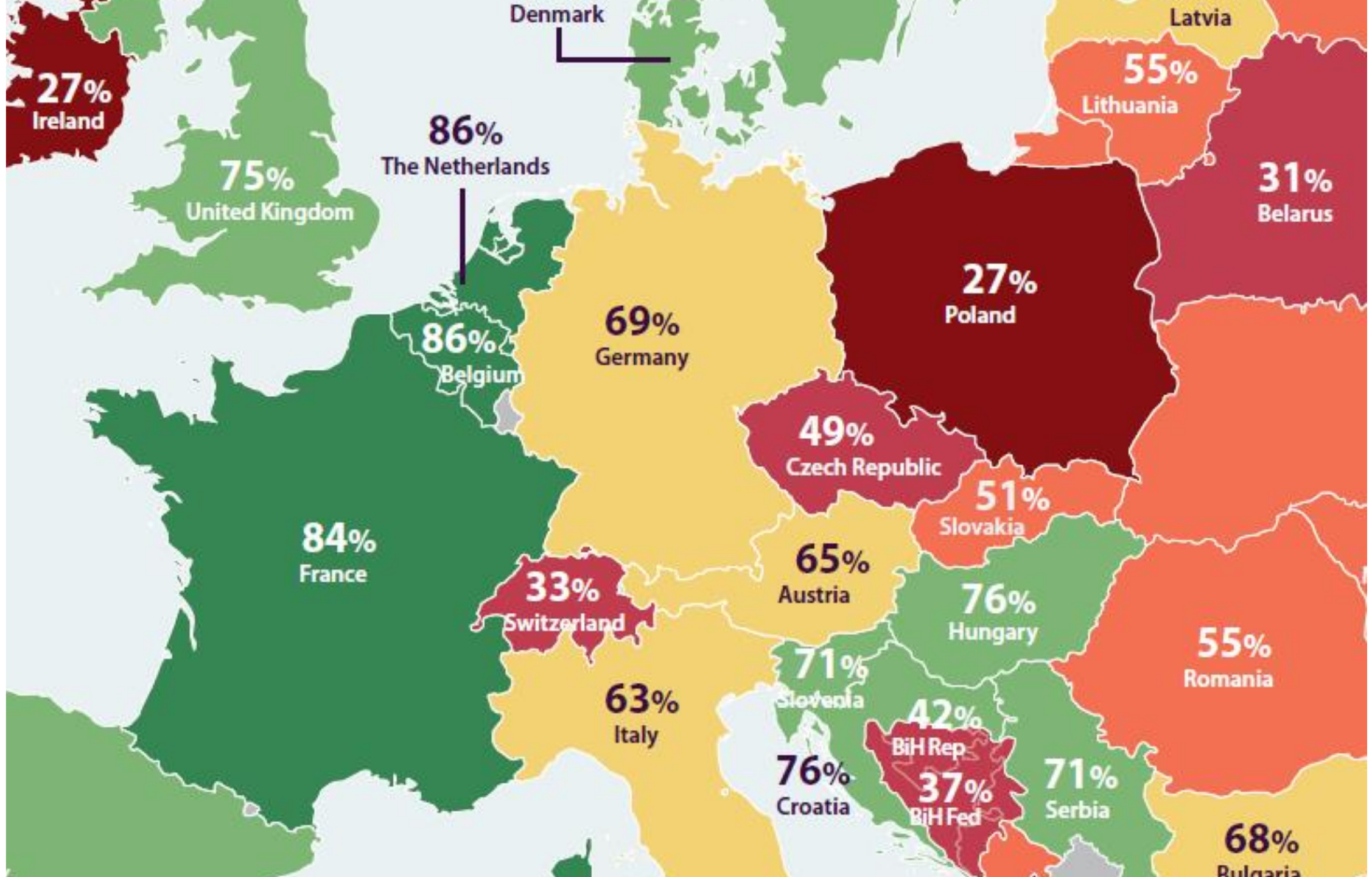
JOIN OUR CALL TO ACTION AT [HTTPS://FERTILITYEUROPE.EU/CTA/](https://fertilityeurope.eu/cta/)

## EUROPEAN ATLAS OF FERTILITY TREATMENT POLICIES

DECEMBER 2021



			LEGISLATION		PUBLIC FUNDING/REIMBURSEMENT			PATIENTS PERSPECTIVE			
			REGULATIONS		IUI <sup>(6)</sup> Up to 6 funded	IVF <sup>(3)</sup> /ICSI <sup>(4)</sup> up to 6 funded	Is funding even across the country?	Does infertility patients association get consulted on public policies?	Is psychological support offered as part of MAR <sup>(7)</sup> treatment?	Is there state organised/ sponsored fertility education programme?	
			Is there ART <sup>(1)</sup> law?	National registry of ART <sup>(1)</sup> activity							
	A perfect country	100%	yes (8)	yes (3)	full (6)	full (35)	yes (4)	yes (3)	yes (3)	yes (4)	A perfect country
	Albania	13%	no (0)	no (0)	no (0)	no (0)	-	-	-	-	Albania
	Armenia	26%	yes (8)	no (0)	no (0)	no (0)	-	no (0)	no (0)	state organised (2)	Armenia
	Austria	65%	yes (8)	yes (3)	no (0)	partial (26)	yes (4)	no (0)	one for failed IVF (1)	no (0)	Austria
	Belarus	31%	yes (8)	yes (3)	no (0)	no (0)	no (0)	-	-	-	Belarus
	Belgium	86%	yes (8)	yes (3)	full (6)	partial (32)	yes (4)	yes (3)	partially reimbursed (2)	no (0)	Belgium
	Bosnia & Herzegovina - Fed	37%	yes (8)	yes (3)	no (0)	partial (22)	no (0)	-	-	-	Bosnia & Herzegovina - Fed
	Bosnia & Herzegovina - Rep	42%	yes (8)	yes (3)	no (0)	partial (28)	no (0)	-	-	-	Bosnia & Herzegovina - Rep
	Bulgaria	68%	no (0)	yes (3)	no (0)	partial (31)	yes (4)	sometimes (1)	no (0)	no (0)	Bulgaria
	Croatia	76%	yes (8)	yes (3)	full (6)	partial (33)	yes (4)	sometimes (1)	no (0)	no (0)	Croatia
	Cyprus	59%	yes (8)	no (0)	no (0)	partial (28)	yes (4)	-	-	-	Cyprus
	Czech Republic	49%	yes (8)	yes (3)	no (0)	partial (21)	yes (4)	-	-	-	Czech Republic
					full (6)	partial (30)	no (0)	-	-	-	Denmark
					no (0)	partial (22)	no (0)	-	-	-	Estonia



# «Reproductive Tourism»: Eizellspende in Europa

- Beispiel Spanien (2019): 18.457 Behandlungszyklen für *Patienten aus dem Ausland*
- Kosten pro Zyklus: €5,900-11,000
- Neuerung: «Eizellbanken»



## The current status of oocyte banks: domestic and international perspectives

Alexander M. Quaas, M.D., Ph.D.<sup>a,b,c</sup> and Guido Pennings, Ph.D.<sup>d</sup>

<sup>a</sup> University Hospital, University of Basel, Clinic for Reproductive Medicine and Gynecologic Endocrinology, Basel, Switzerland; <sup>b</sup> Reproductive Partners San Diego, San Diego, California; <sup>c</sup> Division of Reproductive Endocrinology and Infertility, University of California, San Diego, California; <sup>d</sup> Bioethics Institute Ghent, Department of Philosophy and Moral Sciences, Ghent University, Ghent, Belgium

Two major breakthroughs in the field of assisted reproduction—oocyte donation and oocyte vitrification—have joined forces to create the rapidly emerging phenomenon of commercial egg banks (CEBs). In this review, we examine the history of this concept, the operational models, the geographical variations, and the benefits and pitfalls of CEBs, including the ethical and legal dilemmas arising from gamete mobility. We highlight future directions in the brave new world of third-party reproduction. (Fertil Steril® 2018;110:1203-8. ©2018 by American Society for Reproductive Medicine.)

**Key Words:** Assisted reproductive technology, CEBs, commercial egg banks, egg banking, oocyte cryopreservation, third-party reproduction

**Discuss:** You can discuss this article with its authors and other readers at <https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/36448-26514>



# Internationale (z.T. transatlantische) Kontroversen: Beispiele

EFFICACY OF SUPEROVULATION AND INTRAUTERINE INSEMINATION IN THE TREATMENT OF INFERTILITY

EFFICACY OF SUPEROVULATION AND INTRAUTERINE INSEMINATION IN THE TREATMENT OF INFERTILITY

DAVID S. GATEK, M.D., Ph.D., SANDRA ANH CARROLL, M.D., CHRISTOPH COUFRAN, M.D., Ph.D., JAMES W. OUBRECHT, M.D., Ph.D., PAUL FAYOR LUTWAC, Ph.D., MICHAEL P. SHENKAMP, M.D., JOSEPH A. HILL, M.D., LINDA MACHUGOWSKI, JR., M.D., JOHN E. BUSTON, M.D., STEVEN T. NIKAIKIS, M.D., DONNA L. VOGLI, M.D., Ph.D., AND ROBERT E. CARROLL, M.D., FOR THE NATIONAL COOPERATIVE REPRODUCTIVE MEDICINE NETWORK\*

**ABSTRACT**

**Background:** Induction of superovulation with gonadotropins and intrauterine insemination are frequently used to treat infertility. We conducted a large, randomized, controlled clinical trial of these treatments.

**Methods:** We studied 932 couples in which the woman had no identifiable infertility factor and the man had motile sperm. The couples were randomly assigned to receive intracervical insemination, intrauterine insemination, superovulation and intracervical insemination, or superovulation and intrauterine insemination. Treatment continued for four cycles unless pregnancy was achieved.

**Results:** The 231 couples in the group treated with superovulation and intrauterine insemination had a higher rate of pregnancy (23 percent) than the 234 couples in the intracervical insemination group (18 percent), the 234 couples in the group treated with superovulation and intracervical insemination (19 percent), or the 233 couples in the intracervical insemination group (10 percent). Stratified, discrete-time Cox proportional-hazards analysis showed that the couples in the group treated with superovulation and intrauterine insemination were 3.2 times as likely to become pregnant as those in the intracervical insemination group (95 percent confidence interval, 2.0 to 5.3) and 1.7 times as likely as those in the intracervical insemination group (95 percent confidence interval, 1.2 to 2.5). The couples in the intracervical insemination group and in the group treated with superovulation and intrauterine insemination, in which motile sperm are suspended in culture medium and injected transcervically into the uterine cavity.

\*Superovulation and intrauterine insemination are used alone or in combination for the treatment of unexplained infertility, male-factor infertility, and other cases of infertility in which the woman has an unobstructed genital tract and some ovarian function and the man has motile sperm. Although national data on the cost of these procedures have not been compiled, costs of \$1,200 per cycle for superovulation and of \$500 per cycle for intrauterine insemination are typical. The risks of superovulation include ovarian hyperstimulation,<sup>1</sup> multiple pregnancy,<sup>2</sup> and possibly, an increase in the risk of ovarian cancer.<sup>3</sup>

We report the results of a large, randomized, controlled clinical trial of the efficacy of superovulation and intrauterine insemination.

**METHODS**

**Centers and Subjects**

This study was conducted at 30 clinical sites and was approved by the appropriate institutional review committees at each site. All the couples gave informed consent to participate.

Before enrollment, each couple underwent a standard evaluation for infertility, including semen analysis in the man, antral-follicle biopsy, hysterosalpingiography, and laparoscopy in the woman, and a test for serum antihypertensive antibodies in the couple. Semen analysis was performed according to standardized methods<sup>4</sup> by trained technicians at each center, who followed common protocols and

Human Reproduction, Vol.31, No.12 pp. 2645–2647, 2016  
Advanced Access publication on September 22, 2016 doi:10.1093/humrep/dew241

human reproduction

DEBATE

## IUI and IVF for unexplained subfertility: where did we go wrong?

R.I. Tjon-Kon-Fat<sup>1</sup>, A.J. Bendsdorp<sup>1</sup>, I. Scholten<sup>1</sup>, S. Repping<sup>1</sup>, M. van Wely<sup>1</sup>, B.W.J. Mol<sup>2,3</sup>, and F. van der Veen<sup>1,\*</sup>

<sup>1</sup>Centre for Reproductive Medicine, Academic Medical Centre, University of Amsterdam, 1105 DD Amsterdam, the Netherlands  
<sup>2</sup>The Robinson Research Institute, School of Medicine, University of Adelaide, SA 5000, Adelaide, Australia  
<sup>3</sup>The South Australian Health and Medical Research Unit, SA 5000, Adelaide, Australia

\*Correspondence address. E-mail: f.vanderveen@amc.uva.nl

Submitted on August 1, 2016; resubmitted on August 21, 2016; accepted on August 26, 2016

Human Reproduction Vol.21, No.6 pp. 1337–1344, 2006  
Advance Access publication February 22, 2006

doi:10.1093/humrep/del026

## DEBATE—CONTINUED

### The relative myth of elective single embryo transfer

Norbert Gleicher<sup>1,2,3,5</sup> and David Barad<sup>1,2,4</sup>

<sup>1</sup>Center for Human Reproduction, New York, NY, <sup>2</sup>Foundation for Reproductive Medicine, <sup>3</sup>Department of Obstetrics and Gynecology, Yale University School of Medicine, Chicago, IL and <sup>4</sup>Department of Epidemiology and Social Medicine and Department of Obstetrics and Obstetrics and Gynecology & Women's Health, Albert Einstein College of Medicine, Bronx, NY, USA

<sup>5</sup>To whom correspondence should be addressed at: Center for Human Reproduction, 21 East 69th Street, New York, NY 10021, USA. E-mail: ngleicher@thechr.com

The option of single embryo transfer (SET) has recently dominated the pages of this and other medical journals. Opinions, in regards to the utility of such an approach, appear to differ between Europe and the US. While US guidelines promote a more individualized approach, European opinions, at times, even advocate mandated practice patterns. The European approach, however, fails to recognize the rather significant differences in supportive arguments between the historical switch from multiple embryo transfers to 2-embryo transfers and the current discussion, favouring a switch from 2-embryo transfer to elective (e)-SET. In the former, a significant risk of (at times, high-order) multiple pregnancies was reduced without loss of pregnancy potential. In the latter, a comparably relatively low twinning risk is reduced in treatment success preference of some inf e-SET, as has been promoted an appropriate transfer SET appears unrealistic

Human Reproduction vol.15 no.8 pp.1662–1665, 2000

DEBATE continued

Key words: embryo transfer, Avoiding multiple pregnancies in ART

Replace as many embryos as you like—one at a time

Allan Templeton<sup>1</sup>

Department of Obstetrics & Gynaecology, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen AB25 2ZD, Scotland, UK

<sup>1</sup>To whom correspondence should be addressed at: Department of Obstetrics & Gynaecology, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen AB25 2ZD, Scotland, UK. E-mail: allan.templeton@abdn.ac.uk

This debate was previously published on Webtrack, May 17, 2000

There has been much concern over the years about the health of children born following assisted reproduction and whether they are at increased risk of abnormality. Most recently this concern has focused around children born to infertile fathers following intracytoplasmic sperm injection (ICSI) and a number of important follow-up studies are underway. However any putative risks in this respect pale into insignificance when compared with the morbidity in children born of high order multiple pregnancy. Even twins, generally regarded as a happy outcome of IVF, run increased risks of divine or endine un

So what more can be done. In the UK, to be fair, there has been some movement. The number of two-embryo replacements is increasing, but there is no evidence yet of a fall in multiple birth rates and particularly triplet rates. There are considerable regional variations in practice, undoubtedly influenced by the provision of care and the views of opinion leaders. Several private clinics in London generate more triplets in 1 year than does the whole of Scotland. Recent guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) recommending two-embryo replacements in all women aged <40 years seem destined to be ignored unless adopted by Health Authorities. British Fertility Society recommendations have been in place for some time, but have had little effect. The Human Fertilisation and Embryology Authority (HFEA) seems reluctant to interfere with 'clinical freedom', although it does have a concern for the welfare of the child.

Colleagues in Scandinavia have yet again shown the way forward (Hazekamp *et al.*, 2000) and are already into a serious discussion about one-embryo replacement (in attitude and practice, they seem light years ahead of the situation in the UK). If good embryo cryopreservation rates can be maintained or improved, then one-embryo replacement must be the way forward. In the long run, it may be the best thing not just from the point of view of mother and child, but also of the father.

- Intrauterine Insemination bei «unexplained infertility»
- Single embryo transfer
- PGT-A (Aneuploidie-Screening von Embryonen)
- Ovarielle Stimulationsprotokolle
- Auftauzyklen: Protokolle und Medikamente etc. etc.

# “Social Freezing”

## Elective Oocyte Cryopreservation (EOC)

---

### Struktur

---

Was ist «Social Freezing» (EOC)?

Gesellschaftliche Trends

Technische Aspekte

Outcome data

Take-home points

---

---

---

---

---

---

---

---

---

---

# Planned Oocyte Cryopreservation (OC)

ASRM PAGES



## Evidence-based outcomes after oocyte cryopreservation for donor oocyte in vitro fertilization and planned oocyte cryopreservation: a guideline

The Practice Committee of the American Society for Reproductive Medicine  
The American Society for Reproductive Medicine, Birmingham, Alabama

- Freiwillige und selbstbestimmte Oozyten-Kryopräservaion zum Anlegen einer persönlichen (nicht Partner-bezogenen) Fertilitätsreserve
- Zweck: Oozyten-Kryo erhält die Eizellen-Qualität auf dem jetzigen Stand (zum Zeitpunkt des Einfrierens), zur späteren Verwendung
- Ziel: Gewinnung der rekrutierten Antral-Follikel (Eibläschen) in einem Zyklus (die ansonsten zugrunde gehen würden)

# Fallstudie: Brigitte Adams

- “Poster woman” für egg freezing
- Im Alter von 39: als «Single» Marketing Consultant 11 Oozyten kryokonserviert
- Titelstory (Bloomberg): «Later, Baby: Will Freezing Your Eggs Free Your Career?»
- Untertitel: «Egg freezing technology is helping women kiss the mommy track goodbye»





Sections 

The Washington Post  
*Democracy Dies in Darkness*

National

Climate

Education

Health

Innovations

Investigations

National Security

Obituaries

Science

Abortion

# The struggle to conceive with frozen eggs

Brigitte Adams became the poster child for freezing your eggs. But things didn't quite work out how she imagined.



# Fallstudie: Brigitte Adams

- Im Alter von 44: (weiterhin «Single»)  
Auftauen der Oozten, Befruchtung mit  
Samenspende
- Von 11 Oozyten:
  - 9 nach Auftauen überlebt
  - 6 befruchtet
  - 1 Blastozyste
- Embryo Transfer: keine Schwangerschaft
- (Behandlung mit Eizellspende: erfolgreich)

NATIONAL POST



World / News



## Cruel twist of fate for single woman who froze her eggs in her 30s to 'free her career'

*Last year, with her 45th birthday looming and no sign of Mr. Right, Brigitte Adams excitedly unfroze the 11 eggs and selected a sperm donor*

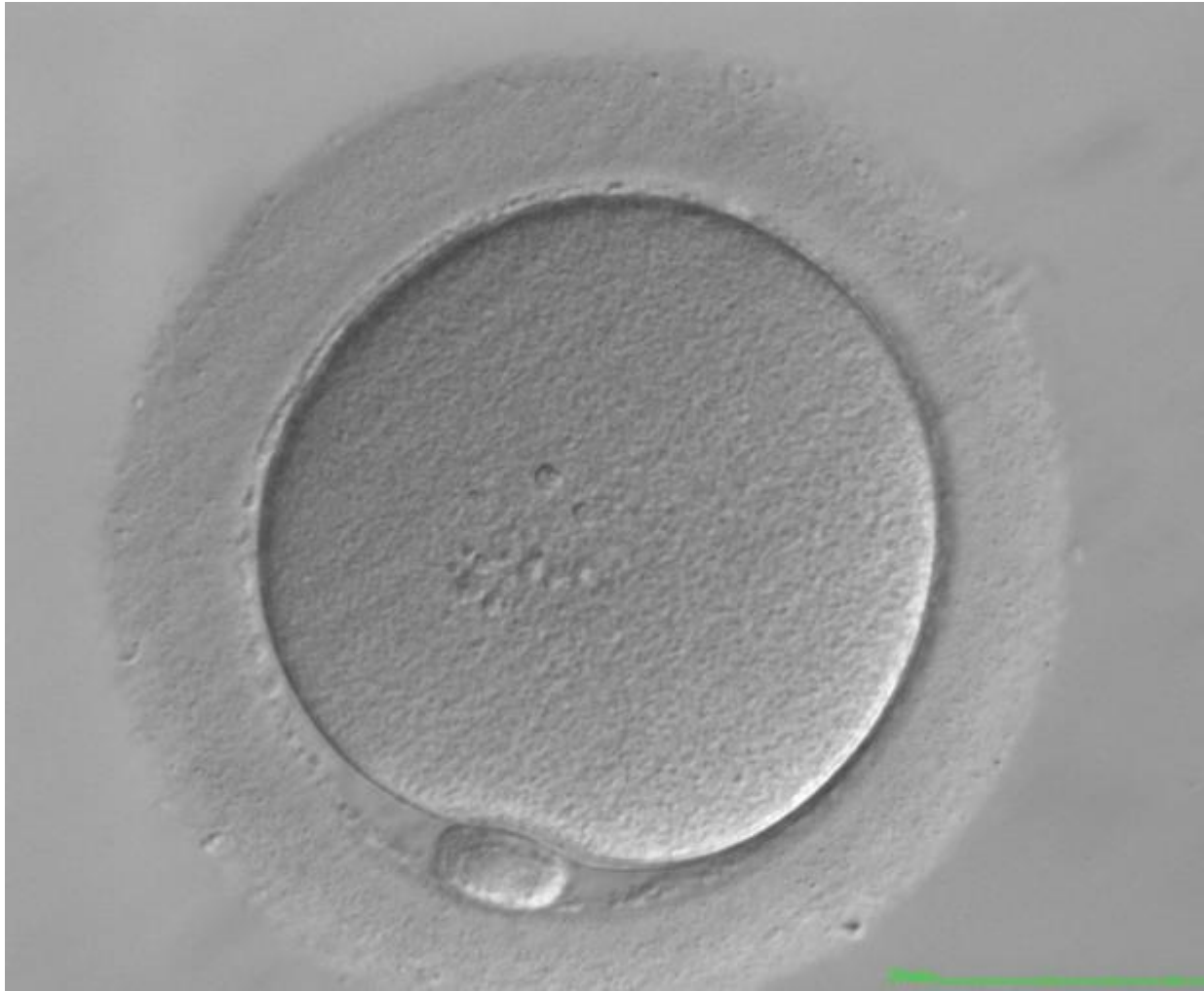
Ariana Eunjung Cha, Washington Post

Jan 29, 2018 • January 29, 2018 • 12 minute read • [Join the conversation](#)



Brigitte Adams holds sonogram prints of her pregnancy at the Center for Fetal Medicine in Los Angeles. PHOTO BY CAROLYN VAN HOUTEN/WASHINGTON POST

# Die Herausforderung



# ASRM Eilmeldung 2012

**Embargoed for Release: Monday, October 22, 2012 – 12:01 AM Eastern Daylight Time**

## **Fertility Experts Issue New Report on Egg Freezing; ASRM Lifts “Experimental” Label from Technique**

*San Diego, CA* - The Practice Committee of the American Society for Reproductive Medicine (ASRM) issued a new report today stating that in young patients egg freezing techniques have been shown to produce pregnancy rates, leading to the birth of healthy babies, comparable to IVF cycles using fresh eggs.



ASRM PAGES

## Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental. This document replaces the document last published in 2008 titled, "Ovarian Tissue and Oocyte Cryopreservation," Fertil Steril 2008;90:S241-6. (Fertil Steril® 2013;99:37-43. ©2013 by American Society for Reproductive Medicine.)

**Earn online CME credit related to this document at [www.asrm.org/elearn](http://www.asrm.org/elearn)**

**Discuss:** You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/goldsteinj-mature-oocyte-cryopreservation-guideline/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.\*

\* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

ASRM PAGES

## Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental. This document replaces the document last published in 2008 titled, "Ovarian Tissue and Oocyte Cryopreservation," Fertil Steril 2008;90:S241-6. (Fertil Steril® 2013;99:37-43. ©2013 by American Society for Reproductive Medicine.)

**Earn online CME credit related to this document at [www.asrm.org/elearn](http://www.asrm.org/elearn)**

**Discuss:** You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/goldsteinj-mature-oocyte-cryopreservation-guideline/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.\*

\* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

# Mehrere RCTs an «frischen» und vitrifiziert / aufgetauten Eizellen: vergleichbare Ergebnisse

**TABLE 1**

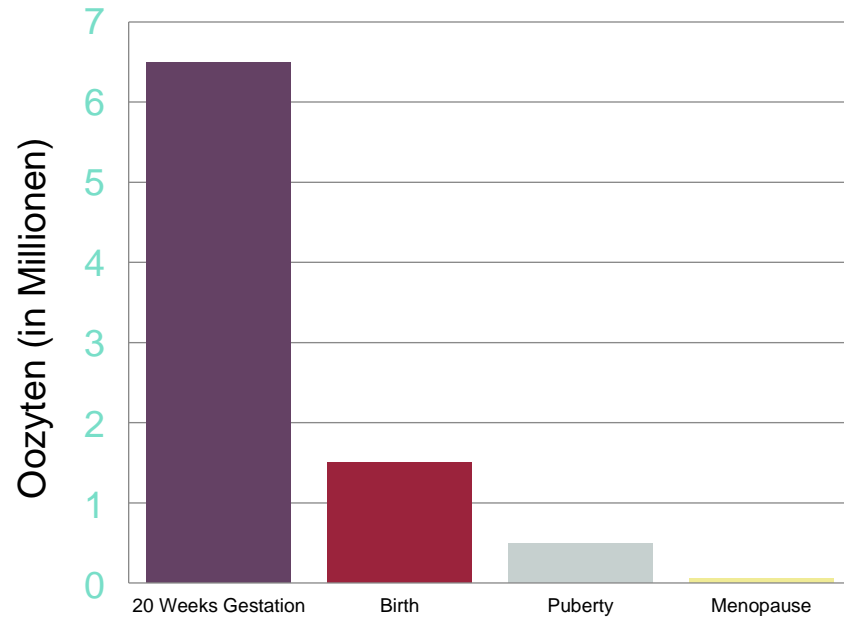
Summary of randomized controlled trials comparing fresh versus vitrified oocytes.

	Cobo 2008 (24)	Cobo 2010 (26)	Rienzi 2010 (25)	Parmegiani 2011 (19)
Patient population	Oocyte donors	Oocyte donors	Infertile patients <43 years of age requiring ICSI with >6 mature oocytes	Infertile patients <42 years of age requiring ICSI with >5 mature oocytes
No. patients	30 vitrification 30 fresh	295 vitrification 289 fresh	40 vitrification 40 fresh	31 vitrification 31 fresh
Mean age at retrieval	26	26	35	35
No. oocytes	231 vitrification 219 fresh	3286 vitrification 3185 fresh	124 vitrification 120 fresh	168 vitrification NA fresh
No. oocytes per retrieval	18.2	11	13	NA
Survival	96.9%	92.5%	96.8%	89.9%
Fertilization rate	76.3 vitrification 82.2 fresh	74% vitrification 73% fresh	79.2% vitrification 83.3% fresh	71% vitrification 72.6% fresh
No. transferred vitrification vs. fresh	3.8 vitrification 3.9 fresh	1.7 vitrification 1.7 fresh	2.3 vitrification 2.5 fresh	2.5 vitrification 2.6 fresh
Day of transfer	3	3	2	2–3
Implantation rate	40.8% vitrification 100% fresh	39.9% vitrification 40.9% fresh	20.4% vitrification 21.7% fresh	17.1% vitrification NA fresh
CPR/transfer vitrification vs. fresh	60.8% (23 vitrification transfers) 100% (1 fresh transfer)	55.4% vitrification 55.6% fresh	38.5% vitrification 43.5% fresh	35.5% vitrification 13.3% fresh
CPR/oocyte thawed	6.1%	4.5%	12%	6.5%

Note: All used vitrification with Cryotop, 15% EG + 15% DMSO + 0.5M sucrose. CPR = clinical pregnancy rate.

Practice Committee. Oocyte cryopreservation. *Fertil Steril* 2013.

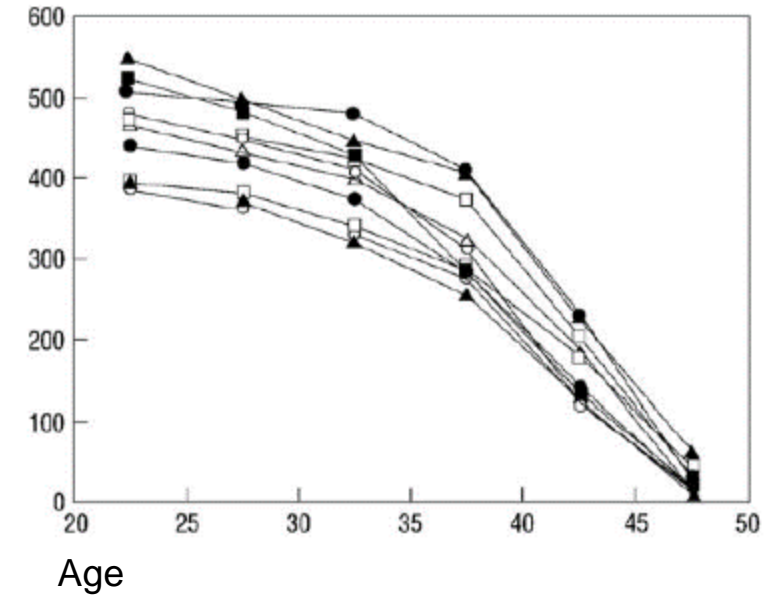
# Abnahme der Ovarialreserve



- In utero: Eizellen-Maximum
- Keine Neubildung
  - 20 SSW: circa 6-7 Millionen
  - Geburt: 1-2 Millionen
  - Pubertät: 500.000
  - Menopause: 100-1000
- Reproduktionsjahre einer Frau:  
Circa 400 ovulierte Oozyten

# Reproduktives Altern

- Der reproduktive Alterungsprozess beginnt bereits Anfang 20
- Aber: Konzeptionsraten weiterhin hoch in Frauen im Alter von 30-35
- >35: beschleunigte Abnahme von Eizell- Quantität und Qualität
- Mit 45: SS-Potenzial fast 0
- ↑ Raten von Abortgeschehen und genetischen Aberrationen



Quelle: ACOG and ASRM. Age-related fertility decline.

# Trends

- Demographische Veränderungen
- Medien-Berichte über Oozyten-Kryokonservierung
- Bewusstsein, dass durch Technologie der Alterungsprozess aufgehalten werden kann
- Prominente Befürworter
- Firmen im "Silicon Valley": Kostenübernahme



«Guardian»  
Oktober 2014

Apple

## Apple and Facebook offer to freeze eggs for female employees

Facebook will pay up to \$20,000 while Apple will provide perk from January in effort to attract more women

Mark Tran

@marktran

Wed 15 Oct 2014 09:57 BST



▲ Egg storage for IVF. Apple and Facebook are to offer the perk alongside other benefits for staff. Photograph: Science Photo Library/Getty Images

Apple and Facebook are offering to freeze eggs for female employees in an effort to attract more women on to their staff.

Apple, the world's most valuable brand, said it would offer the perk to US-based staff from January.

"Apple cares deeply about our employees and their families, and we are always looking at new ways our health programmes can meet their needs," said the company.

"We continue to expand our benefits for women, with a new extended maternity leave policy, along with cryopreservation and egg storage as part of our extensive support for infertility treatments ... We want to empower women at Apple to do the best work of their lives as they care for loved ones and raise their families."

Apple's move follows the appointment of Denise Young Smith as head of human resources in February. She is making a big push on diversity and inclusion at the iPhone-maker.

The offer to freeze eggs is among initiatives that include longer parental leave, education reimbursements for all classes taken by employees and subsidised student loan refinancing.

In an effort to attract and retain talent, Young Smith has asked Apple's 98,000 employees to find out what kind of benefits they care most about.

Facebook offers up to \$20,000 (£13,000) for egg freezing for female employees. The company also offers adoption and surrogacy assistance and "a host of other fertility services for male and female employees", the company said.

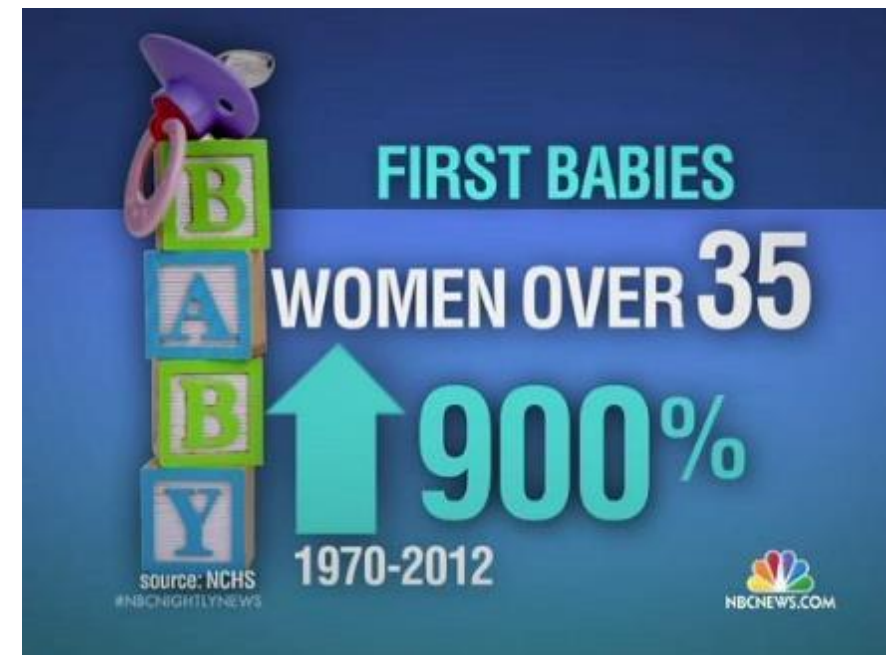
A typical round of egg freezing costs about \$10,000, with \$500 or more in fees each year for storage. Two rounds are usually necessary to harvest about



Sign up for Guardian Today US edition: the day's must reads sent directly to you.

# Sozialer Trend: Verschiebung des KiWu als «new normal»

- Zwischen 1970 und 2012: 900% Anstieg in der Anzahl der Frauen mit erstem Kind >35
- 35% Anstieg Altersgruppe 40-44
- “Social Freezing” als “Versicherung”?



Mai 2014; [www.cdc.gov](http://www.cdc.gov)



## What do reproductive-age women who undergo oocyte cryopreservation think about the process as a means to preserve fertility?

Brooke Hodes-Wertz, M.D., M.P.H.,<sup>a</sup> Sarah Druckenmiller, B.A.,<sup>b</sup> Meghan Smith, M.D.,<sup>a</sup> and Nicole Noyes, M.D.<sup>a</sup>

<sup>a</sup> New York University, Fertility Center at New York University Langone Medical Center, and <sup>b</sup> New York University School of Medicine, New York, New York

**Objective:** To better understand women's beliefs, priorities, and attitudes toward oocyte cryopreservation, to appreciate the extent of their reproductive education, and to track the reproductive paths of women who chose to undergo oocyte cryopreservation treatment.

**Design:** An anonymous 30-question survey.

**Setting:** Not applicable.

**Patient(s):** From 2005–2011, 478 women completed  $\geq 1$  oocyte cryopreservation treatment cycle at our center to defer reproduction.

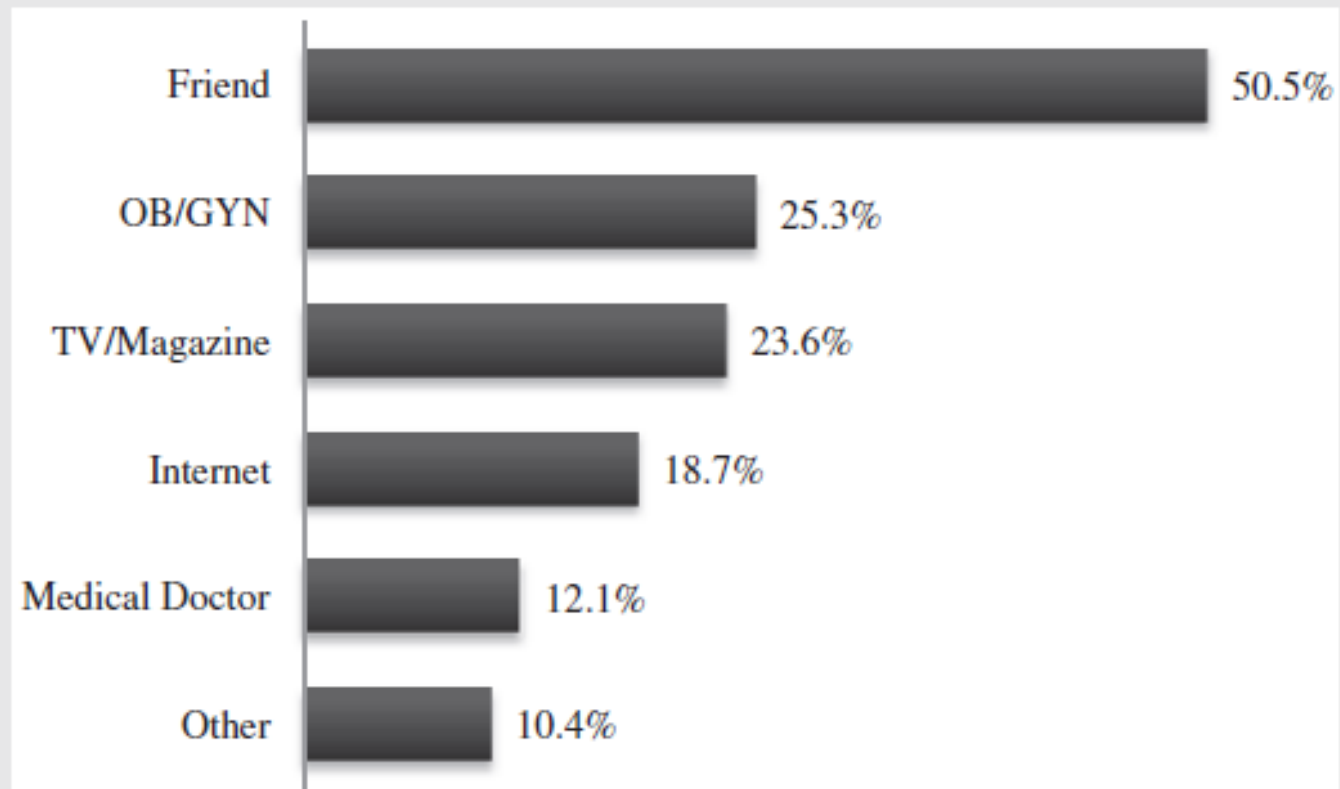
**Intervention(s):** None.

**Main Outcome Measure(s):** Demographics, motivations, desires, fertility knowledge, and outcomes related to oocyte cryopreservation.

**Result(s):** A total of 183 patients (38%) completed the survey with >80% being aged  $\geq 35$  years; white; having no partner at time of oocyte cryopreservation; undergoing oocyte cryopreservation after an optimal reproductive age; feeling they had improved their reproductive future after oocyte cryopreservation and being empowered by the process; aware of age-related infertility; sensing popular media falsely portrayed the upper age limit for natural conception; and recorded lack of partner as the primary rationale for not yet starting a family. Nineteen percent of respondents added that workplace inflexibility contributed to their reproductive dilemma.

«Referral» /  
überweisung

**FIGURE 1**



How patients first learned about oocyte cryopreservation. OB/GYN = obstetric/gynecologist practitioner.

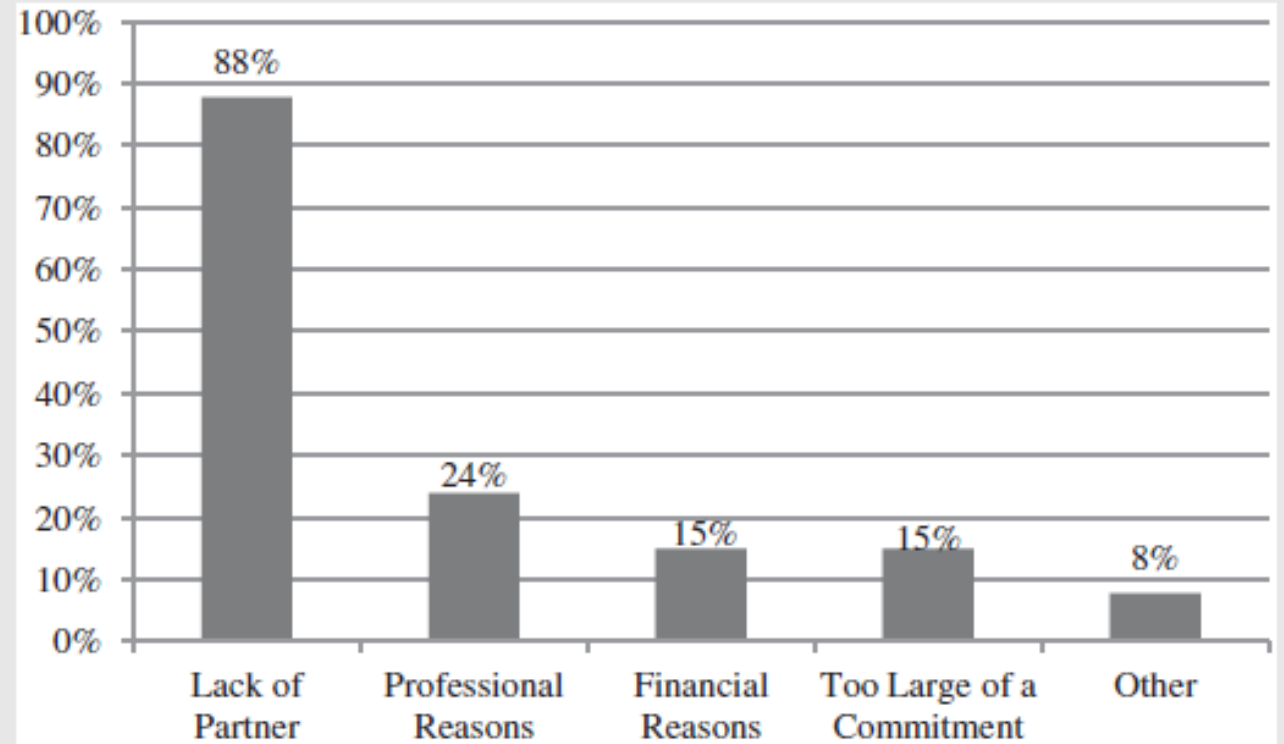
*Hodes-Wertz. What women think about oocyte freezing. Fertil Steril 2013.*

Motive

Aufschiebung

KiWu

**FIGURE 2**

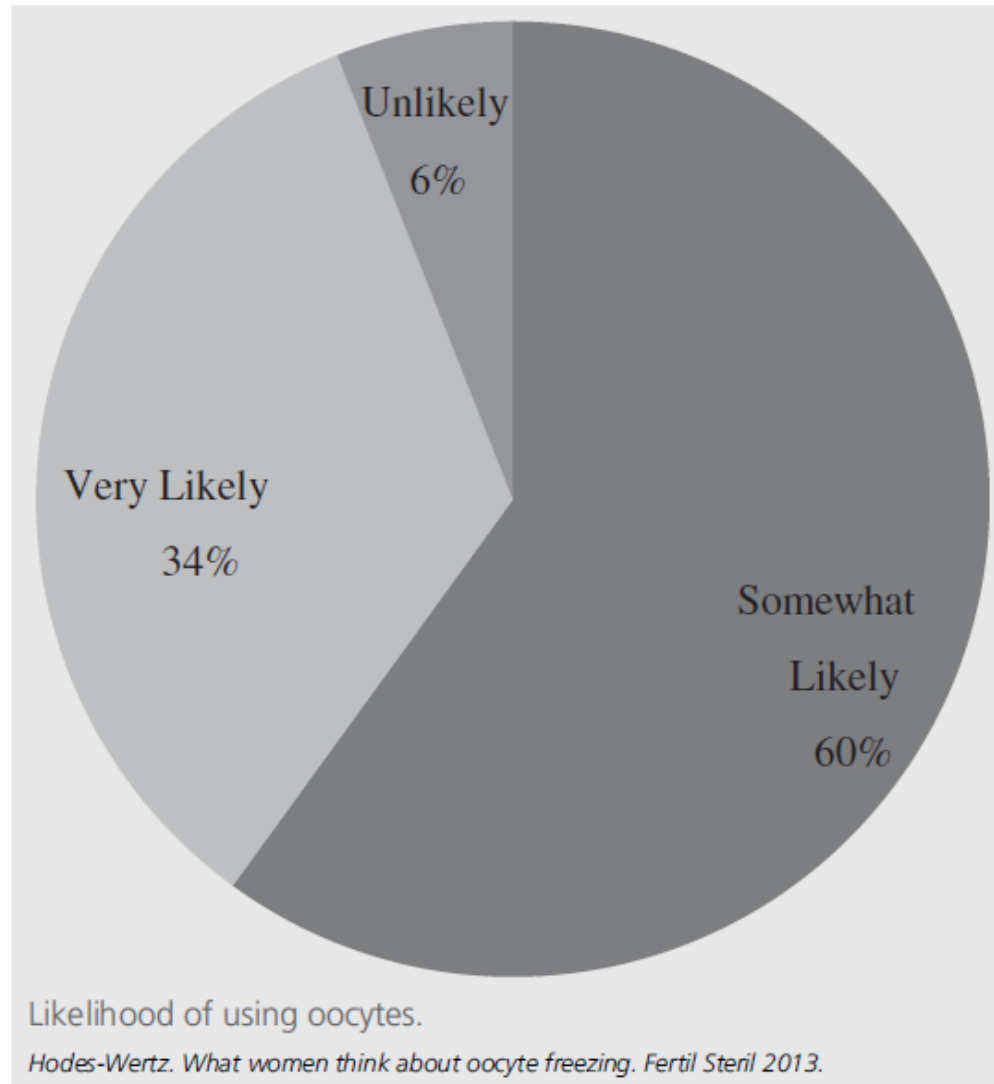


Reasons for not pursuing childbearing earlier.

*Hodes-Wertz. What women think about oocyte freezing. Fertil Steril 2013.*

Einschätzung der  
Wahrscheinlichkeit,  
Oozyten zu verwenden

FIGURE 3



# College-Studenten-Umfrage 2011

## An assessment of female university students' attitudes toward screening technologies for ovarian reserve

Brindha Bavan, B.A.,<sup>a</sup> Ellen Porzig, Ph.D.,<sup>b</sup> and Valerie L. Baker, M.D.<sup>c</sup>

<sup>a</sup> School of Medicine, <sup>b</sup> Department of Developmental Biology, and <sup>c</sup> Department of Obstetrics and Gynecology, Stanford University, Stanford, California

**Objective:** To assess female university students' attitudes toward screening technologies for ovarian reserve and their potential influence on career and family planning decisions.

**Design:** Online survey.

**Setting:** Not applicable.

**Patient(s):** Respondents from 4 universities in Northern California.

**Intervention(s):** None.

**Main Outcome Measure(s):** Proportion with interest in screening technologies for ovarian reserve.

**Result(s):** Of the 328 respondents, 79% were interested in learning about the current status of their ovarian reserve. Hypothetically, if informed that ovarian reserve was very low, 53% would consider oocyte cryopreservation (even

when informed that it is experimental), however, only 29% would consider stopping educational or professional pursuits to focus on conceiving. Participants also demonstrated gaps in knowledge, believing that the decline in ovarian reserve starts later than it actually does, that diet and nutrition can preserve ovarian reserve, and that infertility treatments are highly effective regardless of how severe the depletion of the egg supply is.

**Conclusion(s):** Women attending universities are interested in assessing their own ovarian reserve. Gaps in knowledge about ovarian reserve exist among these reproductive-aged women. (Fertil Steril® 2011;96:1195-9. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Ovarian reserve, egg supply, screening technologies, female university students

## Falsche Vorstellungen:

- Zeitpunkt der Fertilitätsabnahme
- Einfluss Lebensstil (zB. Ernährung)
- Effektivität der Therapien

# “Social Freezing”

## Elective Oocyte Cryopreservation (EOC)

---

### Struktur

---

Was ist «Social Freezing» (EOC)?

Gesellschaftliche Trends

Technische Aspekte

Outcome data

Take-home points

---

---

---

---

---

---

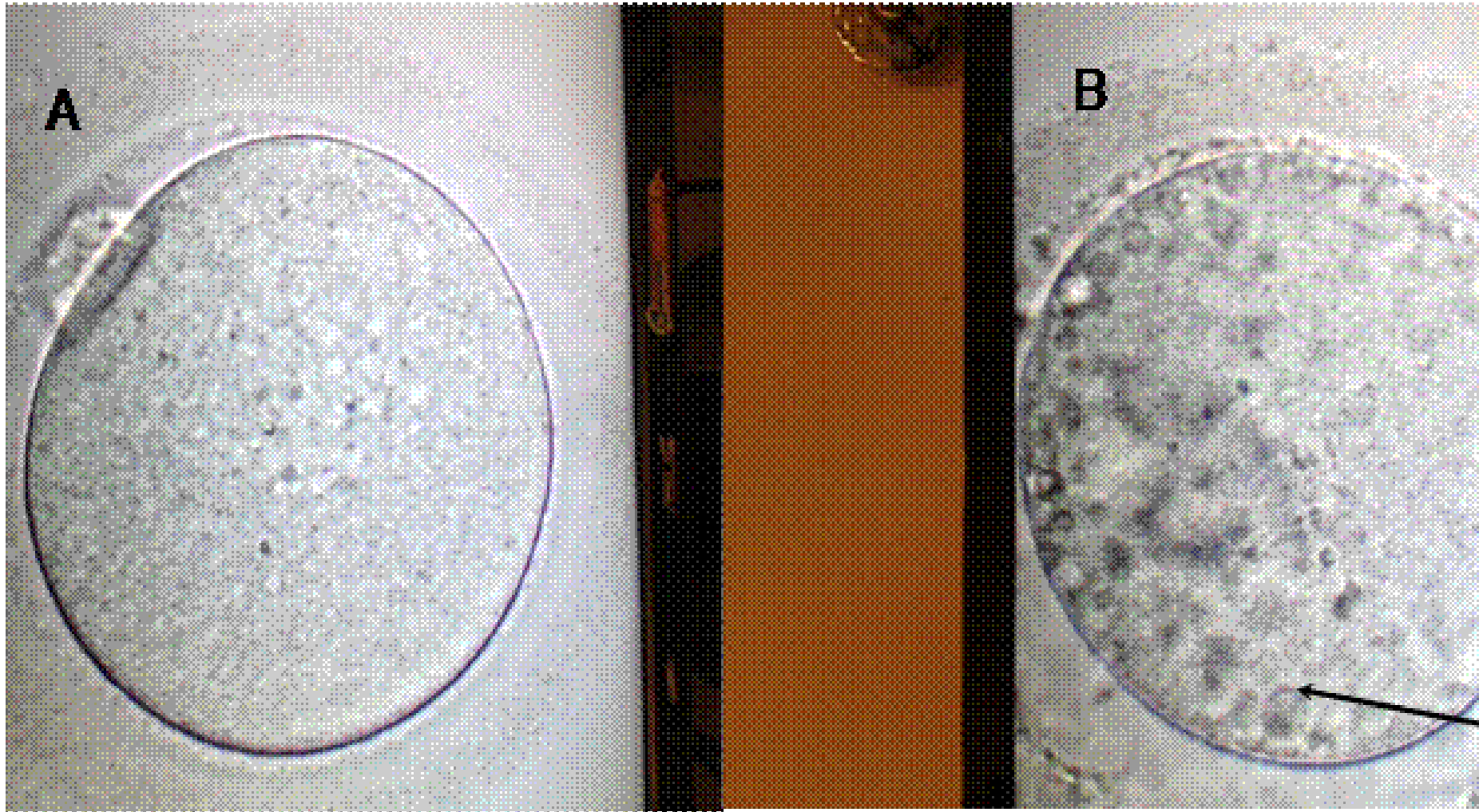
---

---

---

---

# Problem in der Vergangenheit: «Gefrierbrand»



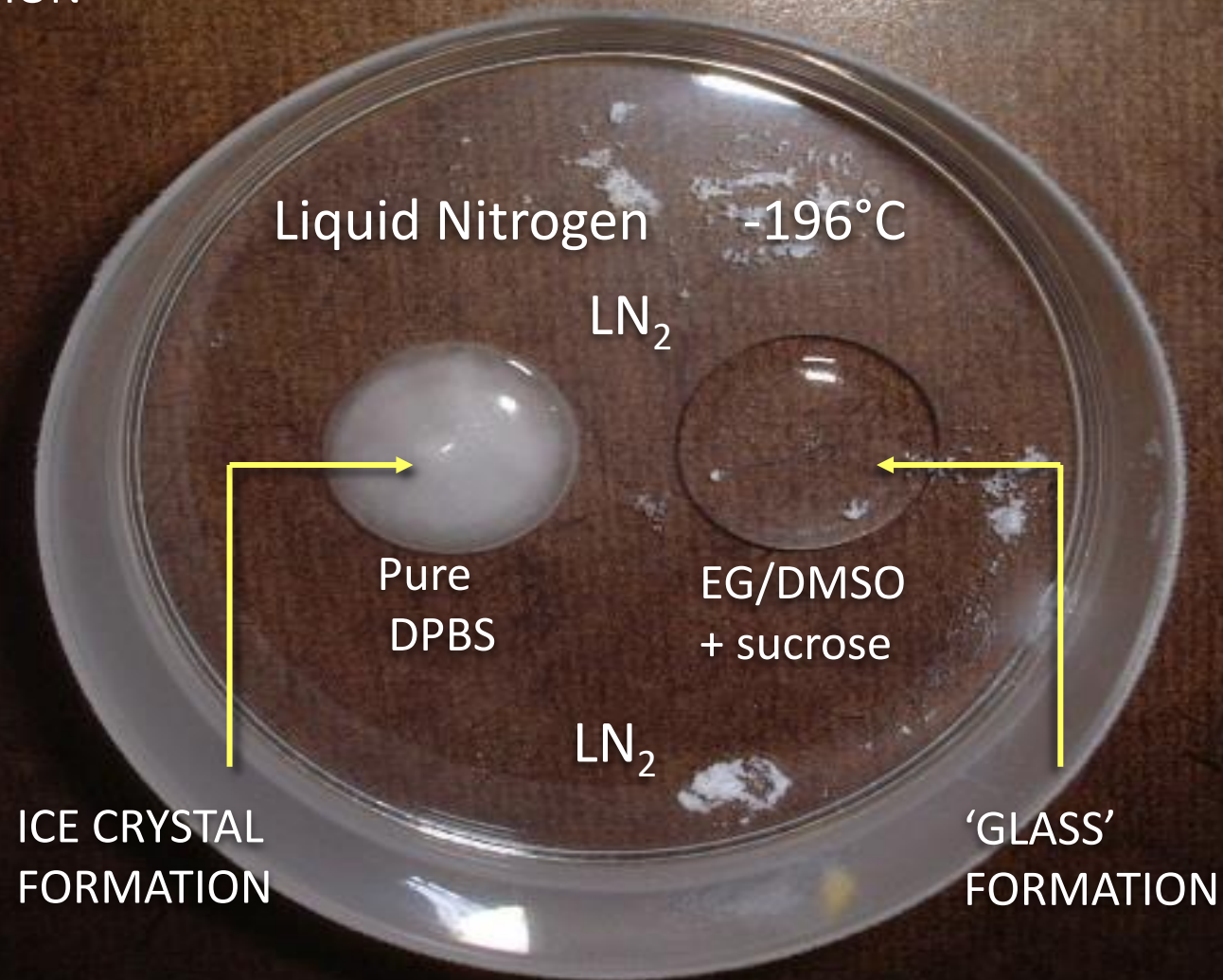
# «Slow Freezing» versus Vitrifikation

Vitrifikation:  
Sehr schnelles Einfrieren,  
glasartiger Zustand





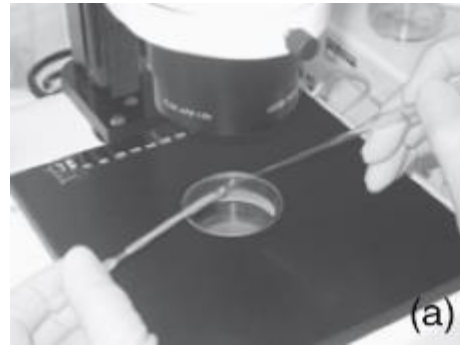
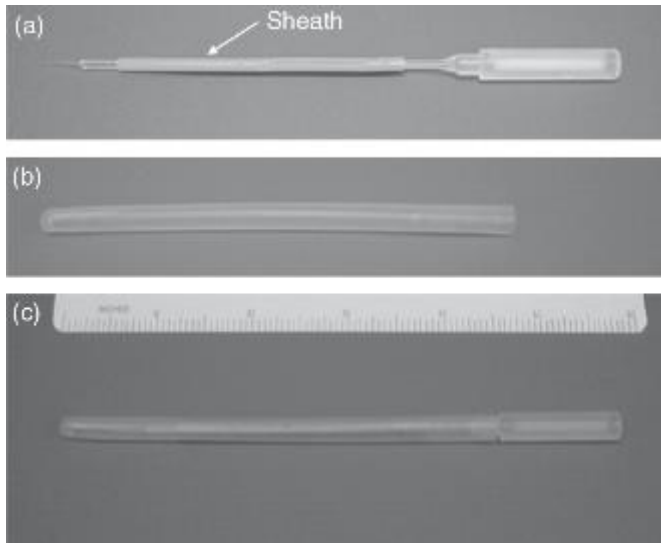
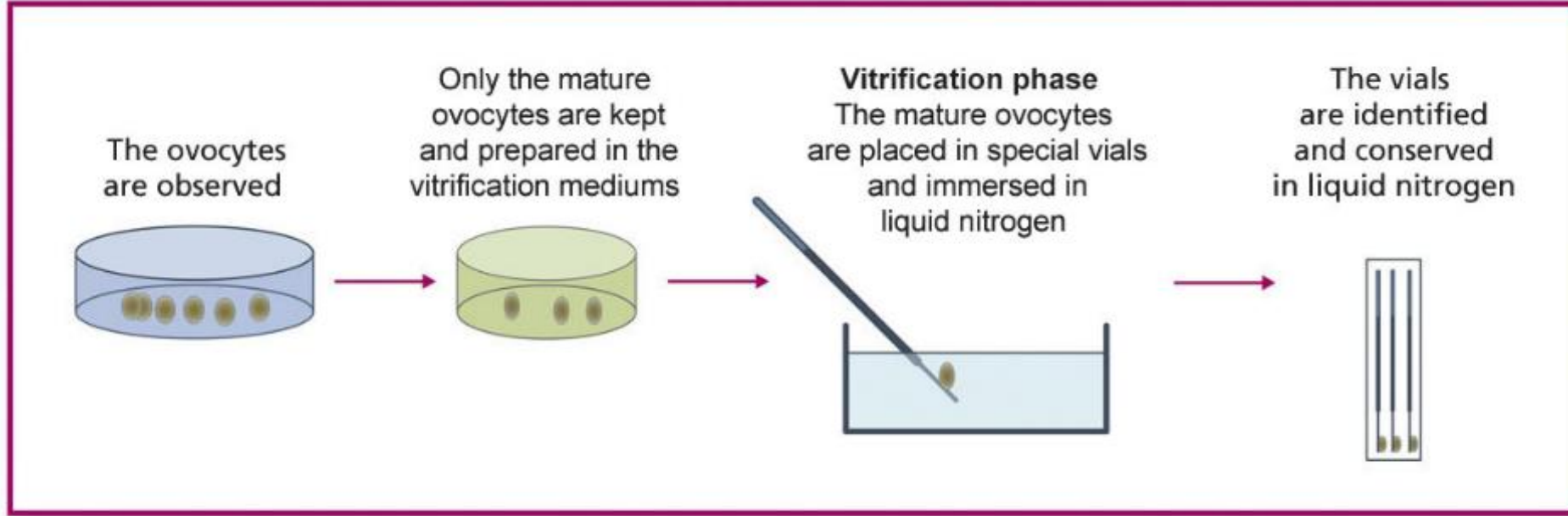
# VITRIFICATION



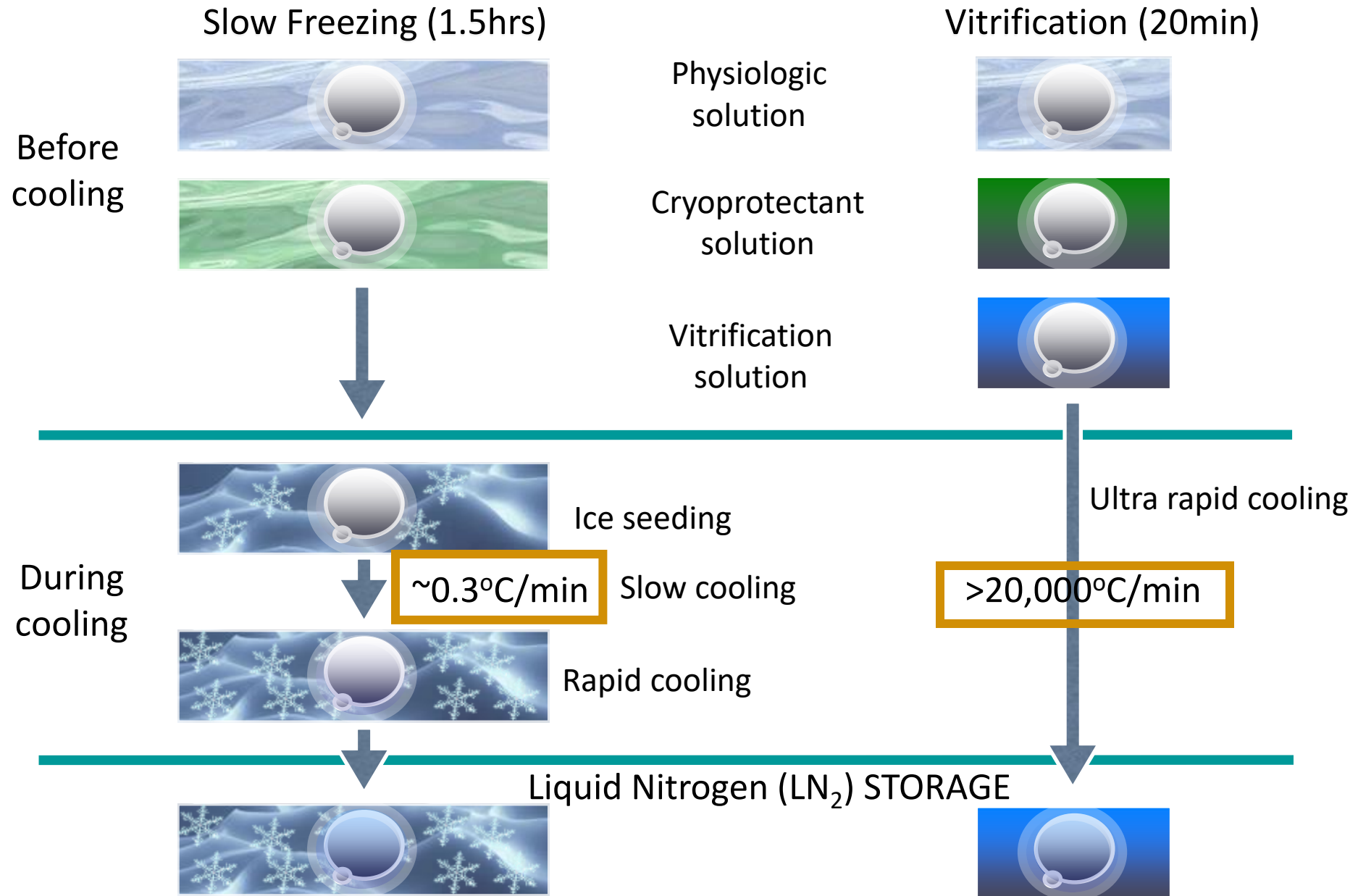
## VITRIFICATION:

solidification of solution (water rapidly cooled & formed into glassy, vitrified state from liquid phase) at low temperature, not by ice crystallization, but by extreme elevation in viscosity during cooling

# Vitrification Technique



# Cryopreservation Techniques



# “Social Freezing”

## Elective Oocyte Cryopreservation (EOC)

---

### Struktur

---

Was ist «Social Freezing» (EOC)?

Gesellschaftliche Trends

Technische Aspekte

Outcome data

Take-home points

---

---

---

---

---

---

---

---

---

---



# Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval

Joseph O. Doyle, M.D., Kevin S. Richter, Ph.D., Joshua Lim, M.S., Robert J. Stillman, M.D., James R. Graham, M.S., and Michael J. Tucker, Ph.D.

Shady Grove Fertility Reproductive Science Center, Rockville, Maryland

Doyle et al.  
F+S 2016

**Objective:** To evaluate a single treatment center's experience with autologous IVF using vitrified and warmed oocytes, including fertilization, embryonic development, pregnancy, and birth outcomes, and to estimate the likelihood of live birth of at least one, two, or three children according to the number of mature oocytes cryopreserved by elective fertility preservation patients.

**Design:** Retrospective cohort study.

**Setting:** Private practice clinic.

**Patient(s):** Women undergoing autologous IVF treatment using vitrified and warmed oocytes. Indications for oocyte vitrification included elective fertility preservation, desire to limit the number of oocytes inseminated and embryos created, and lack of available sperm on the day of oocyte retrieval.

**Intervention(s):** Oocyte vitrification, warming, and subsequent IVF treatment.

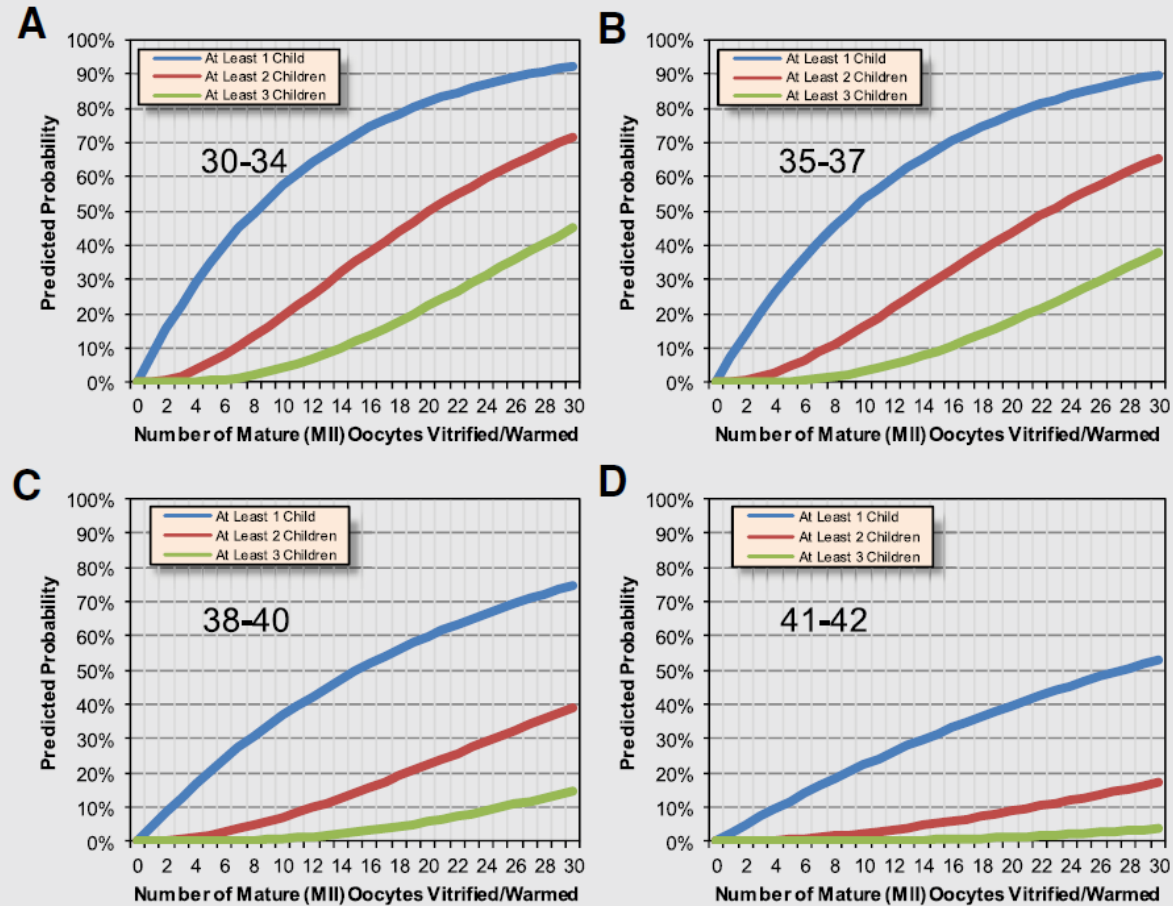
# Materials and Methods

- Retrospektive Kohorten-Studie (SGF)
- Primary outcome: Lebendgeburt-Rate nach Auftauung und Verwendung der Oozyten
- 1283 Oozyten aufgetaut für 128 IVF-Zyklen

*Doyle et al., F&S 2016*

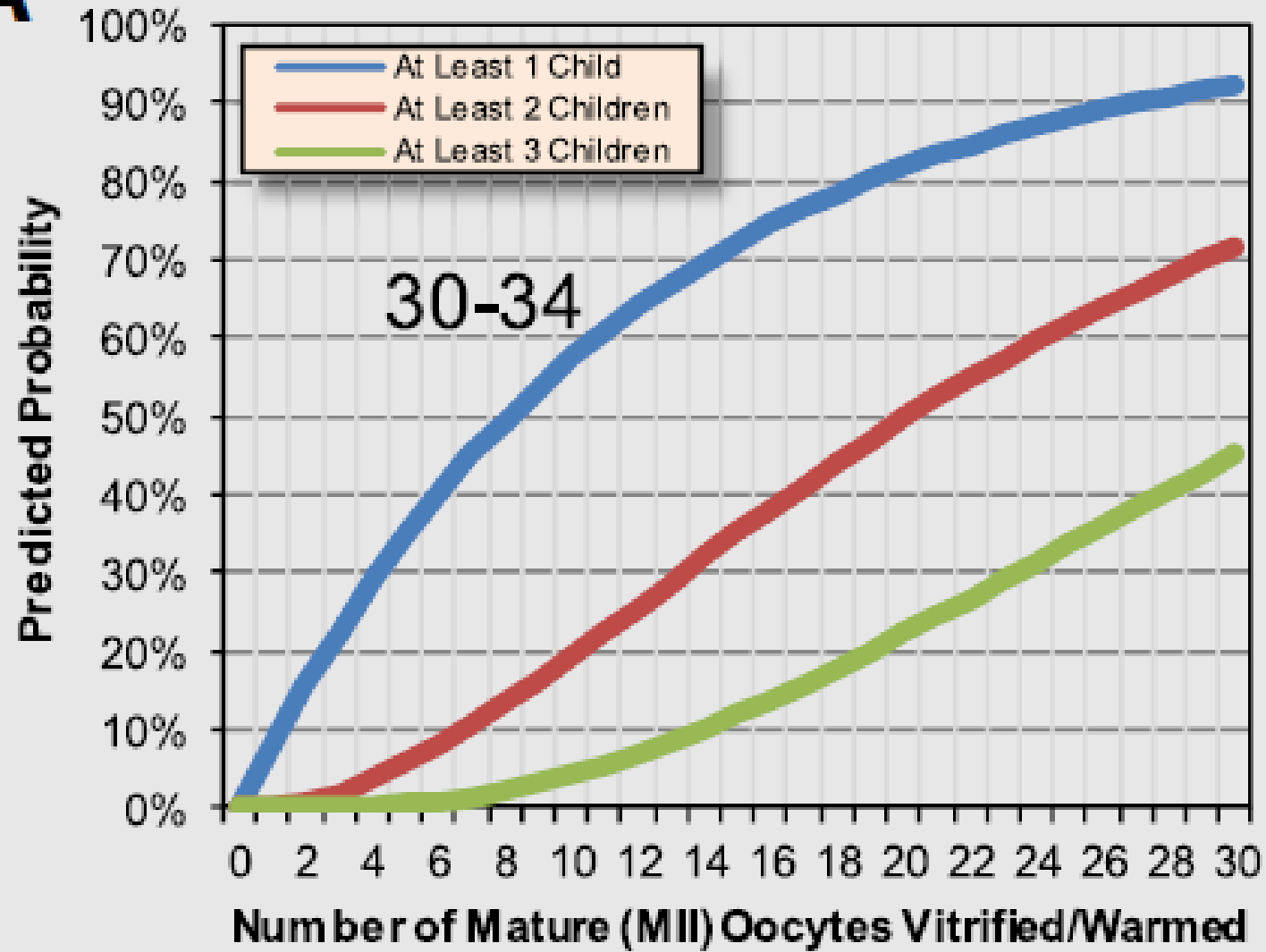
# Geburtswahrscheinlichkeiten

FIGURE 1

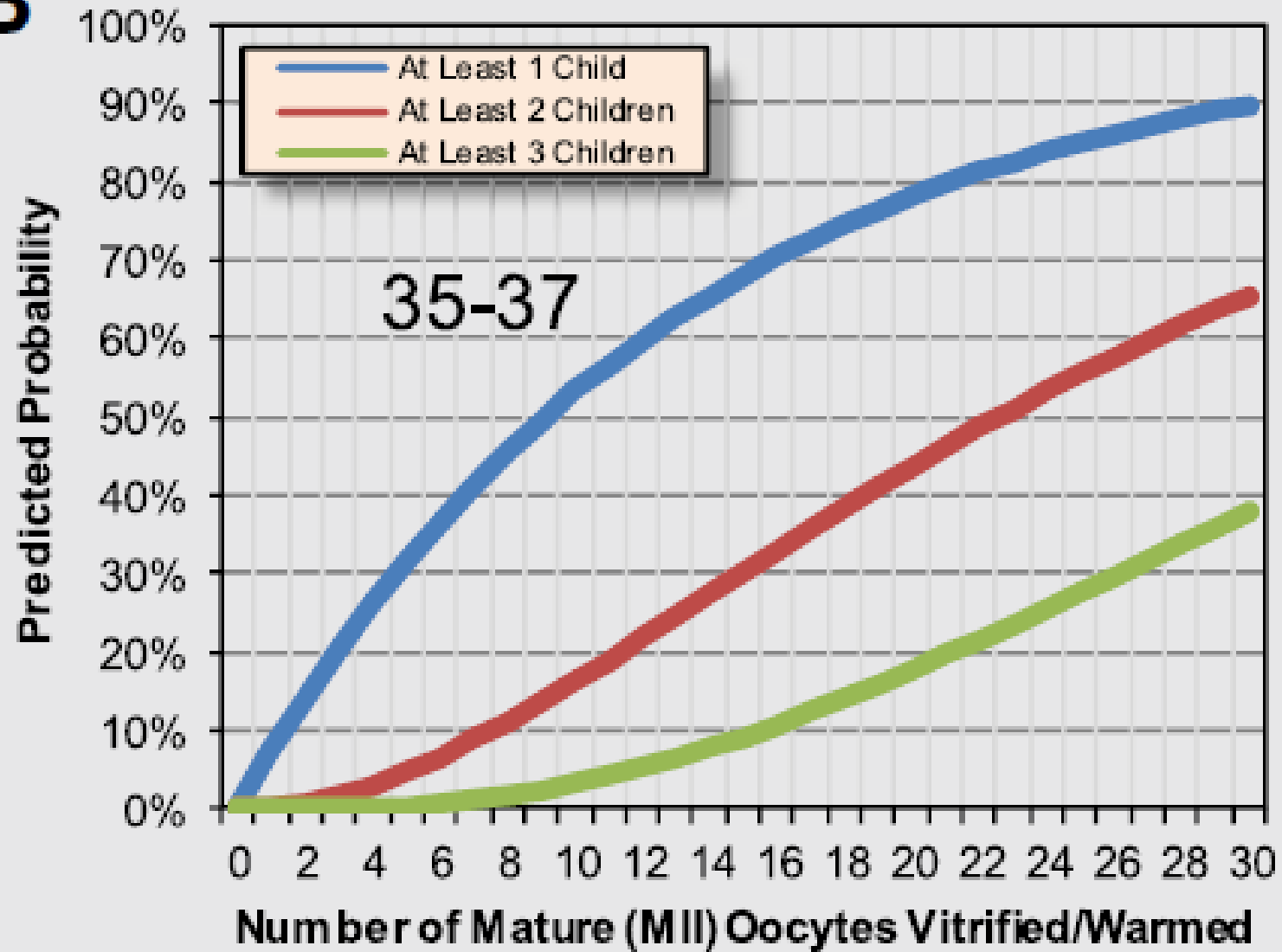


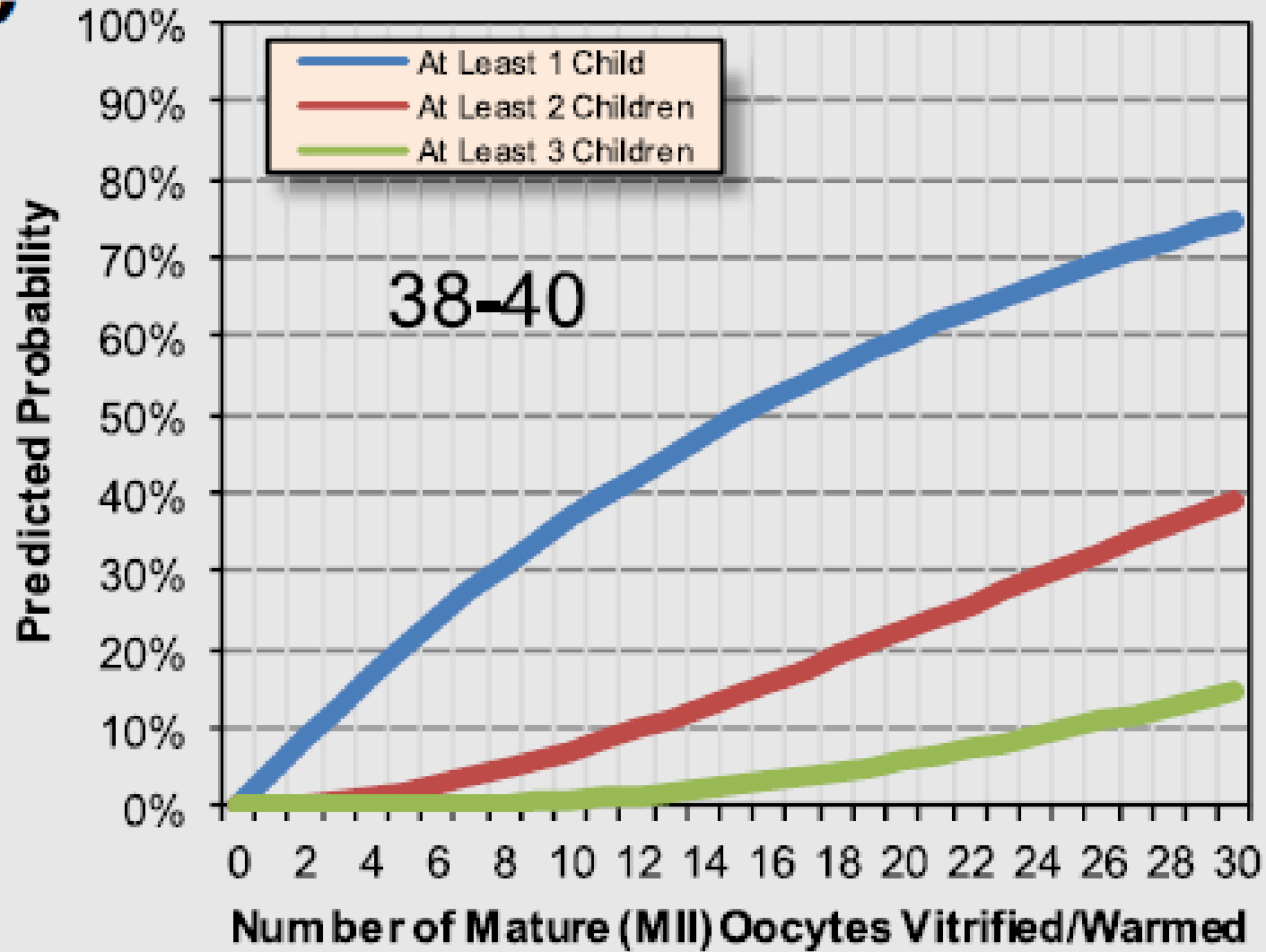
Predicted probabilities of having at least one, two, and three live-born children according to the number of mature oocytes cryopreserved for elective fertility preservation, according to age at oocyte retrieval and the associated oocyte to live-born child efficiency estimates: (A) 30–34 years, 8.2% efficiency; (B) 35–37 years, 7.3% efficiency; (C) 38–40 years, 4.5% efficiency; (D) 41–42 years, 2.5% efficiency.

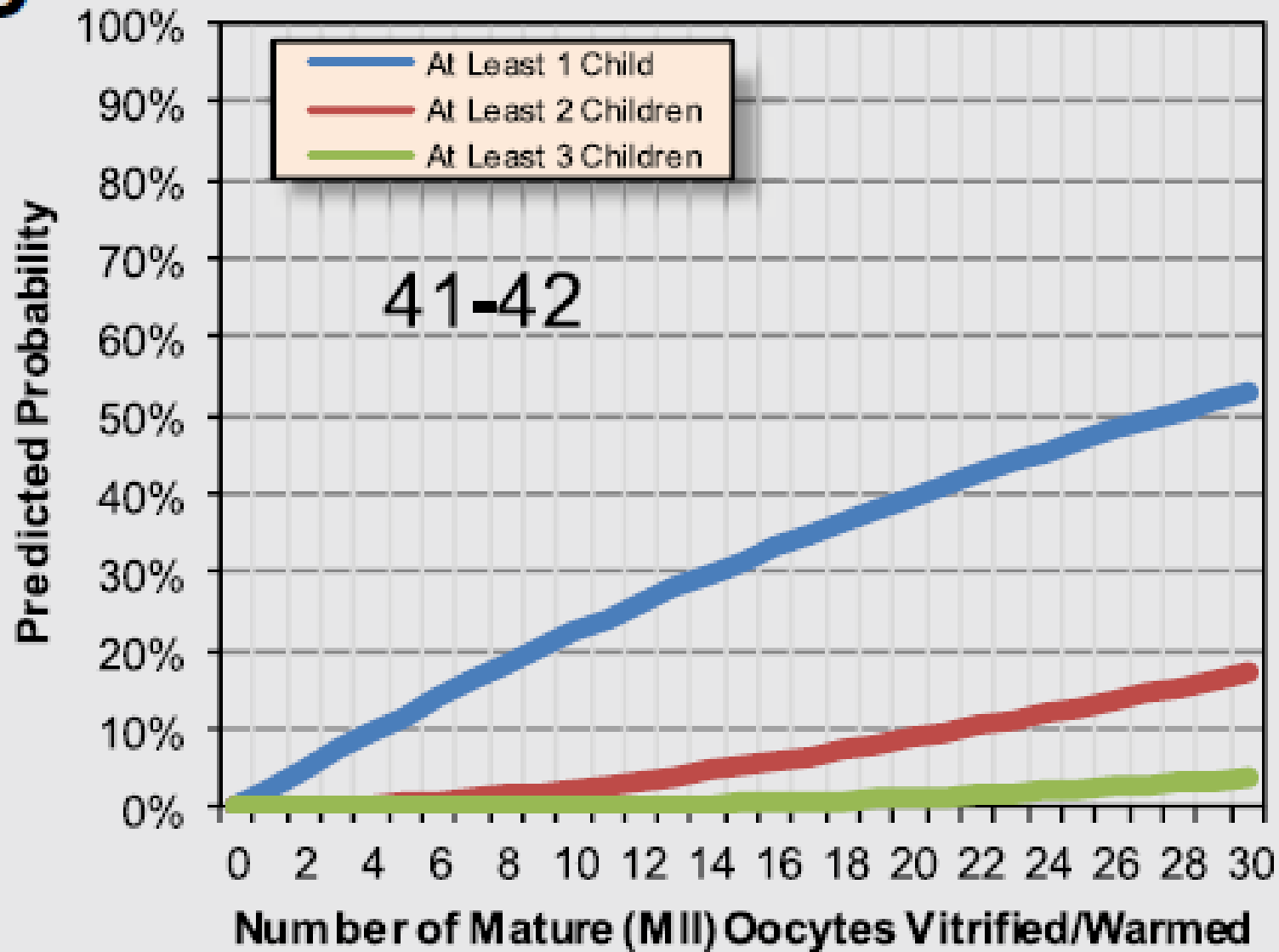
Doyle. Autologous vitrified oocyte IVF outcomes. *Fertil Steril* 2016.

**A**



**B**

**C**

**D**

# «Words of caution»



- “Falsche Versprechung” / Misperception: Eizell-Kryo als “fountain of youth”
  - Vorstellung vieler Frauen: “Menstruation = Fruchtbarkeit”
  - Aber: Infertilität zumeist 10 Jahre vor Menopause
- «Timing» ist sehr wichtig

# 2015 Steiner et al.

ORIGINAL ARTICLES: FERTILITY PRESERVATION



## Optimal timing for elective egg freezing

Tolga B. Mesen, M.D.,<sup>a</sup> Jennifer E. Mersereau, M.D., M.S.C.I.,<sup>a</sup> Jennifer B. Kane, Ph.D.,<sup>b</sup> and Anne Z. Steiner, M.D., M.P.H.<sup>a</sup>

<sup>a</sup> Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, and <sup>b</sup> Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina

**Objective:** To estimate the optimal age to pursue elective oocyte cryopreservation.

**Design:** A decision-tree model was constructed to determine the success and cost-effectiveness of oocyte preservation versus no action when considered at ages 25–40 years, assuming an attempt at procreation 3, 5, or 7 years after initial decision.

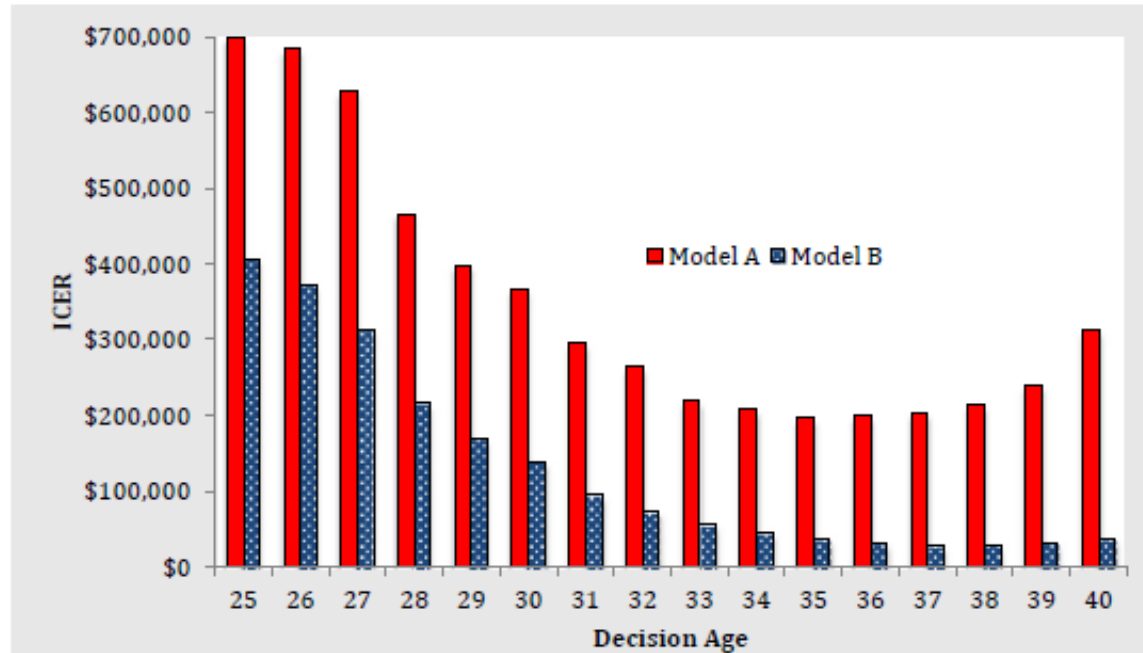
**Setting:** Not applicable.

**Patient(s):** Hypothetical patients 25–40 years old presenting to discuss elective oocyte cryopreservation.

**Intervention(s):** Decision to cryopreserve oocytes from age 25 years to age 40 years versus taking no action.

**Main Outcome and Measure(s):** Probability of live birth after initial decision whether or not to cryopreserve oocytes.

**FIGURE 3**



Cost per additional live birth at horizon age when electing to cryopreserve oocytes versus no action at decision age, which is presented on the x axis. Model A represents women requiring marriage before attempting pregnancy. Model B represents women who do not require marriage before attempting pregnancy (will attempt pregnancy with husband, donor sperm, or unmarried male partner).

*Mesen. Timing of elective egg freezing. Fertil Steril 2015.*

# Bestes Alter laut Modell: 37

**Result(s):** Oocyte cryopreservation provided the greatest improvement in probability of live birth compared with no action (51.6% vs. 21.9%) when performed at age 37 years. The highest probability of live birth was seen when oocyte cryopreservation was performed at ages <34 years (>74%), although little benefit over no action was seen at ages 25–30 years (2.6%–7.1% increase). Oocyte cryopreservation was most cost-effective at age 37 years, at \$28,759 per each additional live birth in the oocyte cryopreservation group. When the probability of marriage was included, oocyte cryopreservation resulted in little improvement in live birth rates.

**Conclusion(s):** Oocyte cryopreservation can be of great benefit to specific women and has the highest chance of success when performed at an earlier age. At age 37 years, oocyte cryopreservation has the largest benefit over no action and is most cost-effective. (Fertil Steril® 2015;103:1551–6. ©2015 by American Society for Reproductive Medicine.)

**Key Words:** Elective oocyte cryopreservation, egg freezing, fertility preservation

---

**Discuss:** You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/mesent-timing-elective-egg-freezing/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.\*

\* Download a free QR code scanner by searching for “QR scanner” in your smartphone’s app store or app marketplace.

- «Planned OC» zwischen 2005 und 2009
- n=231 Patientinnen, 280 Zyklen
- Durchschnittsalter 38.2 (23-45)
- 3250 Eizellen (Durchschnitt 10 reife / Entnahme)
- Primary outcome: disposition
  - 88 Patientinnen: Auftauung / Verwendung (38.1%)
  - 109: weiter gelagert (47.2%)
  - 27: entsorgt (11.7%)
  - 7: woandershin transportiert (3%)

## Planned oocyte cryopreservation— 10–15-year follow-up: return rates and cycle outcomes

Jennifer K. Blakemore, M.D., M.Sc., James A. Grifo, M.D., Ph.D., Shannon M. DeVore, M.D., Brooke Hodes-Wertz, M.D., and Alan S. Berkeley, M.D.

New York University Langone Fertility Center, New York, New York

**Objective:** To evaluate the outcomes of planned oocyte cryopreservation patients most likely to have a final disposition.

**Design:** Retrospective cohort study of all patients who underwent at least 1 cycle of planned oocyte cryopreservation between Jan 2005 and December 2009.

**Setting:** Large urban University-affiliated fertility center

**Patient(s):** All patients who underwent  $\geq 1$  cycle of planned oocyte cryopreservation in the study period.

**Intervention(s):** None

**Main Outcome Measure(s):** Primary outcome was the disposition of oocytes at 10–15 years. Secondary outcomes included thaw/warming types, laboratory outcomes, and live birth rates. Outcomes and variables treated per patient.

**Result(s):** A total of 231 patients with 280 cycles were included. The mean age at the first retrieval was 38.2 years (range 23–45). A total of 3,250 oocytes were retrieved, with an average of 10 metaphase II frozen/retrieval. To date, the oocytes of 88 patients (38.1%) have been thawed/warmed, 109 (47.2%) remain in storage, 27 (11.7%) have been discarded, and 7 (3.0%) have been transported elsewhere. The return rate (patients who thawed/warmed oocytes) was similar by Society for Assisted Reproductive Technology age group. The mean age of patients discarding oocytes was 47.4 years (range, 40–57). Of the 88 patients who thawed/warmed oocytes, the mean age at the time of thaw/warming was 43.9 years (range, 38–50) with a mean of 5.9 years frozen (range, 1–12). Nine patients (10.2%) thawed/warmed for secondary infertility. A total of 62.5% of patients created embryos with a partner, and 37.5% used donor sperm. On average, 14.3 oocytes were thawed/warmed per patient, with 74.2% survival (range, 0%–100%) and a mean fertilization rate of 68.8% of surviving oocytes. Of 88 patients, 39 (44.3%) planned a fresh embryo transfer (ET); 36 of 39 patients had at least 1 embryo for fresh ET, and 11 had a total of 14 infants. Forty-nine of 88 patients (55.7%) planned for preimplantation genetic testing for aneuploidy, with a mean of 4.2 embryos biopsied (range, 0–14) and a euploidy rate of 28.9%. Of the 49 patients, 17 (34.7%) had all aneuploidy or no embryos biopsied. Twenty-four patients underwent a total of 36 single euploid ET with 18 live births from 16 patients. Notably, 8 PGT-A patients had a euploid embryo but no ET, affecting the future cumulative pregnancy rate. Overall, 80 patients with thaw/warming embryos had a final outcome. Of these, 20 had nothing for ET (arrested/aneuploid), and of the 60 who had  $\geq 1$  ET, 27 had a total of 32 infants, with a live birth rate of 33.8% (27/80).

**Conclusion(s):** We report the final outcomes of patients most likely to have returned, which is useful for patient counseling; a utilization rate of 38.1% and a no-use rate of 58.9%, similar across age groups. Further studies with larger cohorts as well as epidemiologic comparisons to patients currently cryopreserving are needed. (Fertil Steril® 2021;115:1511–20. ©2021 by American Society for Reproductive Medicine.)

**El resumen está disponible en Español al final del artículo.**

**Key Words:** Oocyte freezing, oocyte thaw, oocyte utilization, planned oocyte cryopreservation

**Discuss:** You can discuss this article with its authors and other readers at <https://www.fertsterdialog.com/posts/31687>



# NYU outcome data: Verwendung Oozyten (88 Patientinnen)

- Alter zum Zeitpunkt der Verwendung: 43.9 (38-50)
- Durchschnittlich 5.9 Jahre Kryo (1-12), 14.3 Oozyten aufgetaut
- 62.5%: Spermien von Partner; 37.5%: Donor sperm
- Überlebensrate der Eizellen: 74.2%, fertilization rate 68.8%
- 39 (44.3%) «Frisch-Transfer»; 49 (55.7%) PGT-A – «euploidy rate» 28.9%
- 17 PGT-A Patientinnen: kein Embryo für Transfer, 8: euploid Embryo aber noch kein Transfer

80 Patientinnen mit einem «final outcome»:

- 20 ohne Embryo zum Transfer
- 60 mit  $\geq 1$  Embryo Transfer: 27 mit Lebendgeburt (32 Kinder)
- **Lebendgeburttrate 33.8% (27/80)**

# Neue ASRM guideline zu «planned OC»

- Nicht genug Evidenz, um Lebendgeburtsraten verlässlich vorauszusagen
- Bessere outcomes für jüngere Eizellen
- Neonatale Outcomes: ähnlich wie «frische» Oozyten

ASRM PAGES



## Evidence-based outcomes after oocyte cryopreservation for donor oocyte in vitro fertilization and planned oocyte cryopreservation: a guideline

The Practice Committee of the American Society for Reproductive Medicine  
The American Society for Reproductive Medicine, Birmingham, Alabama

**Objective:** To provide evidence-based recommendations to practicing physicians and others regarding the efficacy of oocyte cryopreservation (OC) for donor oocyte in vitro fertilization and planned OC.

**Methods:** The American Society for Reproductive Medicine conducted a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 1986 to 2018. The American Society for Reproductive Medicine Practice Committee and a task force of experts used available evidence and through consensus developed evidence-based guideline recommendations.

**Main Outcome Measure(s):** Outcomes of interest included live birth rate, clinical pregnancy rate, obstetrical and neonatal outcomes, and factors predicting reproductive outcomes.

**Result(s):** The literature search identified 30 relevant studies to inform the evidence base for this guideline.

**Recommendation(s):** Evidence-based recommendations were developed for predicting the likelihood of live births after planned OC, autologous OC in infertile women, and donor OC, as well as factors that may impact live birth rates. Recommendations were developed regarding neonatal outcomes after using fresh vs. cryopreserved oocytes in cases of autologous or donor oocytes.

**Conclusion(s):** There is insufficient evidence to predict live birth rates after planned OC. On the basis of limited data, ongoing and live birth rates appear to be improved for women who undergo planned OC at a younger vs. older age. Although there are no significant differences in per transfer pregnancy rates with cryopreserved vs. fresh donor oocytes, there is insufficient evidence that the live birth rate is the same with vitrified vs. fresh donor oocytes. Neonatal outcomes appear similar with cryopreserved oocytes compared with fresh oocytes. Future studies that compare cumulative live birth rates are needed. (Fertil Steril® 2021;116:36–47. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

**Key Words:** Planned oocyte cryopreservation, donor oocyte IVF, neonatal outcomes

**Discuss:** You can discuss this article with its authors and other readers at <https://www.fertstertdialog.com/posts/32464>

# Take-home points: «Social Freezing»



- Oocyte cryopreservation (OC): nicht mehr experimentell
- (In erfahrenen Zentren): IVF-Erfolgsraten mit vitrifizierten und “frischen” Eizellen vergleichbar
- Mehr und mehr Outcome Data verfügbar
- Ausgewogene Beratung / Counseling essentiell!

# Take-home points bezüglich Reproduktionsmedizin allgemein

- Seit dem 25. Juli 1978 hat sich viel getan
- Das Spektrum reproduktionsmedizinischer Verfahren wird immer breiter
- Es gibt enorme geografische Unterschiede in der Reproduktionsmedizin
- Spannende Schnittpunkte und Überschneidungen von Wissenschaft, Ethik und anderen Bereichen



Vielen Dank !



# Referenzen

- Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. *Reviews in obstetrics and gynecology*. 2008;1(2):69.
- Quaas AM, Legro RS. Pharmacology of medications used for ovarian stimulation. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2019 Feb 1;33(1):21-33.
- Steptoe, Patrick C., and Robert G. Edwards. "Birth after the reimplantation of a human embryo." *The Lancet* 312.8085 (1978): 366.
- Edwards RG, Steptoe PC, Purdy JM. Establishing full-term human pregnancies using cleaving embryos grown in vitro. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1980 Sep;87(9):737-56.
- Jungheim ES, Meyer MF, Broughton DE. Best practices for controlled ovarian stimulation in in vitro fertilization. In *Seminars in reproductive medicine* 2015 Mar (Vol. 33, No. 02, pp. 077-082). Thieme Medical Publishers.
- European Atlas of Fertility Treatment Policies. From: [www.epfweb.org](http://www.epfweb.org)
- Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni Jr L, Buster JE, Nakajima ST, Vogel DL. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *New England Journal of Medicine*. 1999 Jan 21;340(3):177-83.
- Tjon-Kon-Fat RI, Bendsorp AJ, Scholten I, Repping S, Van Wely M, Mol BW, Van Der Veen F. IUI and IVF for unexplained subfertility: where did we go wrong?. *Human Reproduction*. 2016 Dec 1;31(12):2665-7.

# Referenzen

- Practice Committee of the American Society for Reproductive Medicine. "Evidence-based outcomes after oocyte cryopreservation for donor oocyte in vitro fertilization and planned oocyte cryopreservation: a guideline." *Fertility and Sterility* 116.1 (2021): 36-47.
- <https://www.bloomberg.com/news/articles/2014-04-17/new-egg-freezing-technology-eases-womens-career-family-angst?leadSource=verify%20wall>
- <https://www.eviemagazine.com/post/the-tragic-truth-about-freezing-your-eggs>
- Practice Committee of the American Society for Reproductive Medicine. Mature oocyte cryopreservation: a guideline. *Fertility and sterility*. 2013 Jan;99(1):37-43.
- <https://www.theguardian.com/technology/2014/oct/15/apple-facebook-offer-freeze-eggs-female-employees>
- Hodes-Wertz, Brooke, et al. "What do reproductive-age women who undergo oocyte cryopreservation think about the process as a means to preserve fertility?." *Fertility and sterility* 100.5 (2013): 1343-1349.
- Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. *Fertility and sterility*. 2016 Feb 1;105(2):459-66.
- Mesen TB, Mersereau JE, Kane JB, Steiner AZ. Optimal timing for elective egg freezing. *Fertility and sterility*. 2015 Jun 1;103(6):1551-6.
- Blakemore JK, Grifo JA, DeVore SM, Hodes-Wertz B, Berkeley AS. Planned oocyte cryopreservation—10–15-year follow-up: return rates and cycle outcomes. *Fertility and Sterility*. 2021 Jun 1;115(6):1511-20.